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AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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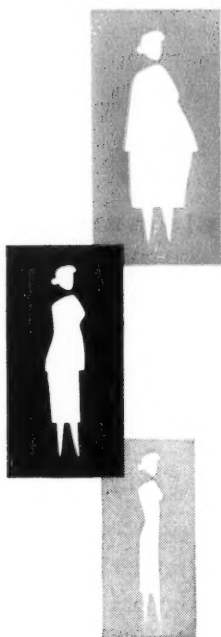
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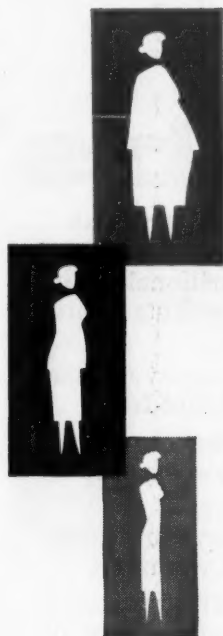
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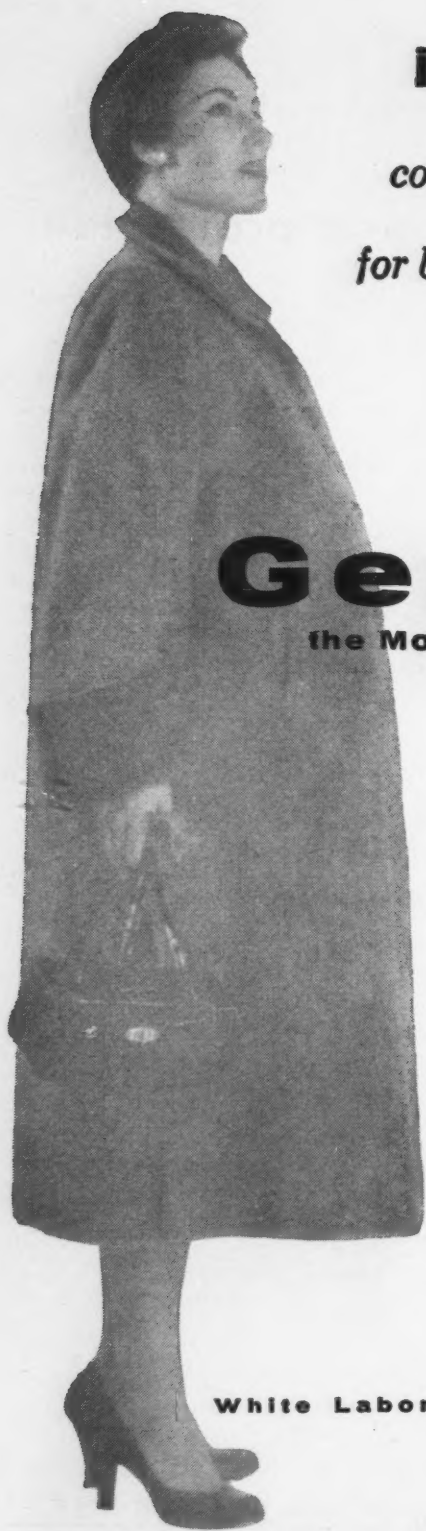
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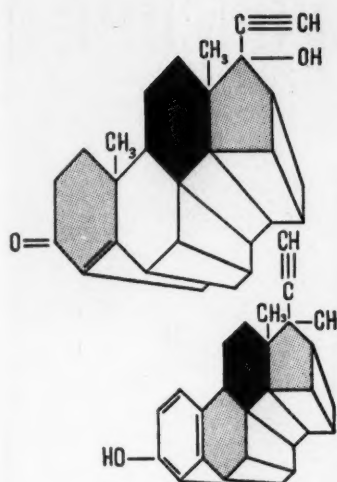
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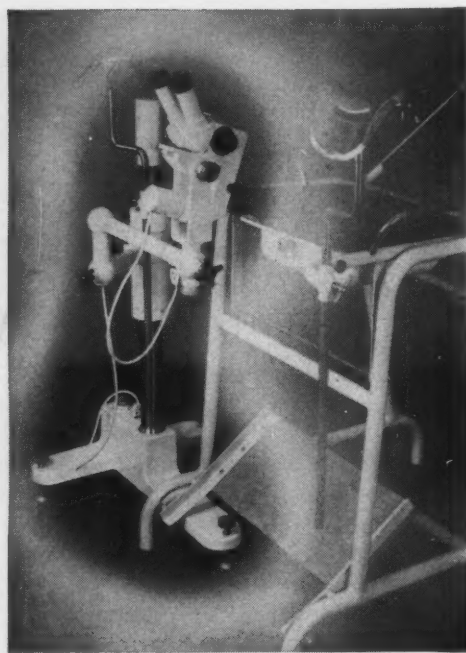
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1. Overall, J. C.: Southern M. J. 47:789, 1954.
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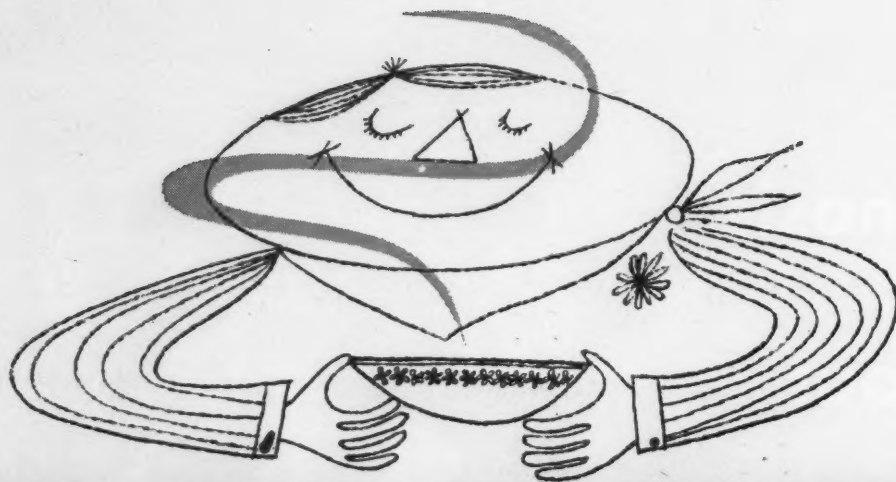


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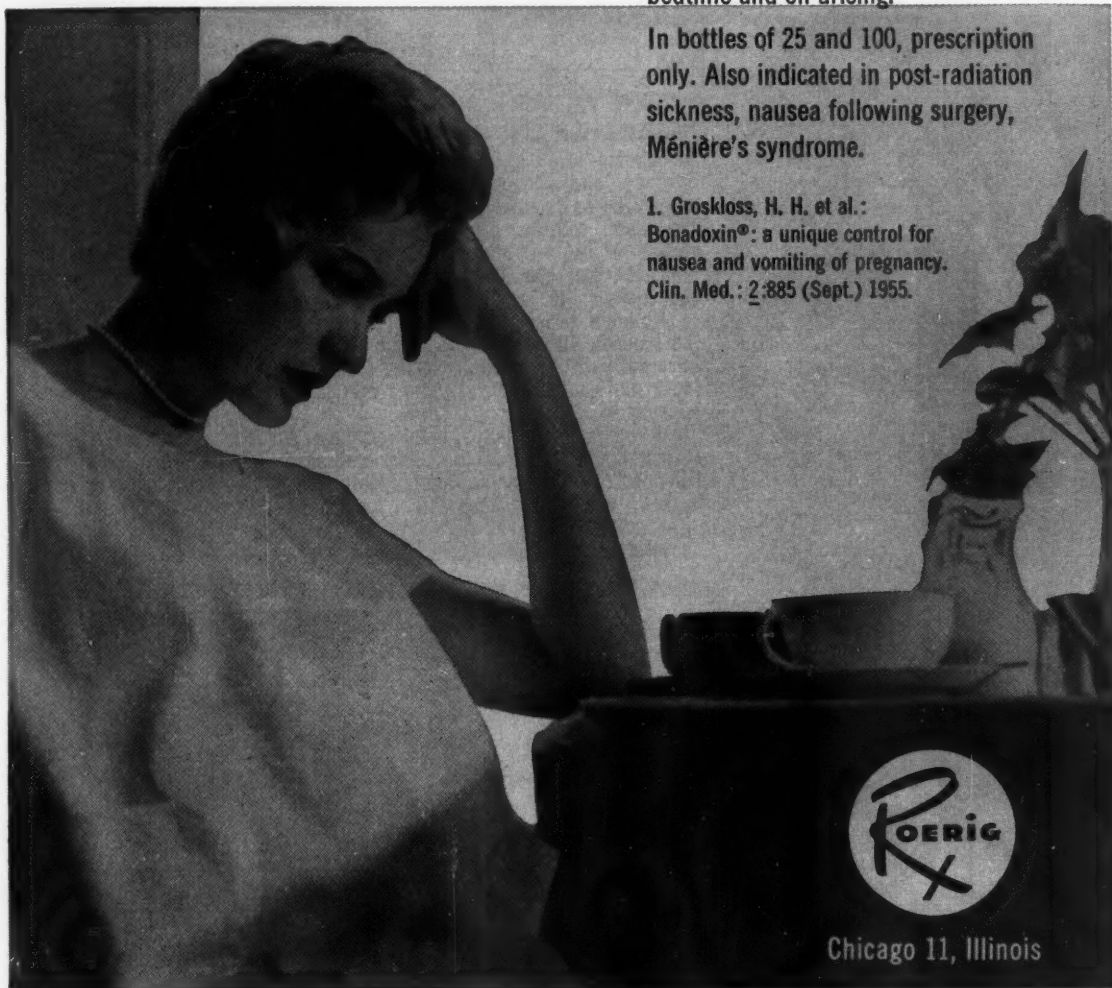
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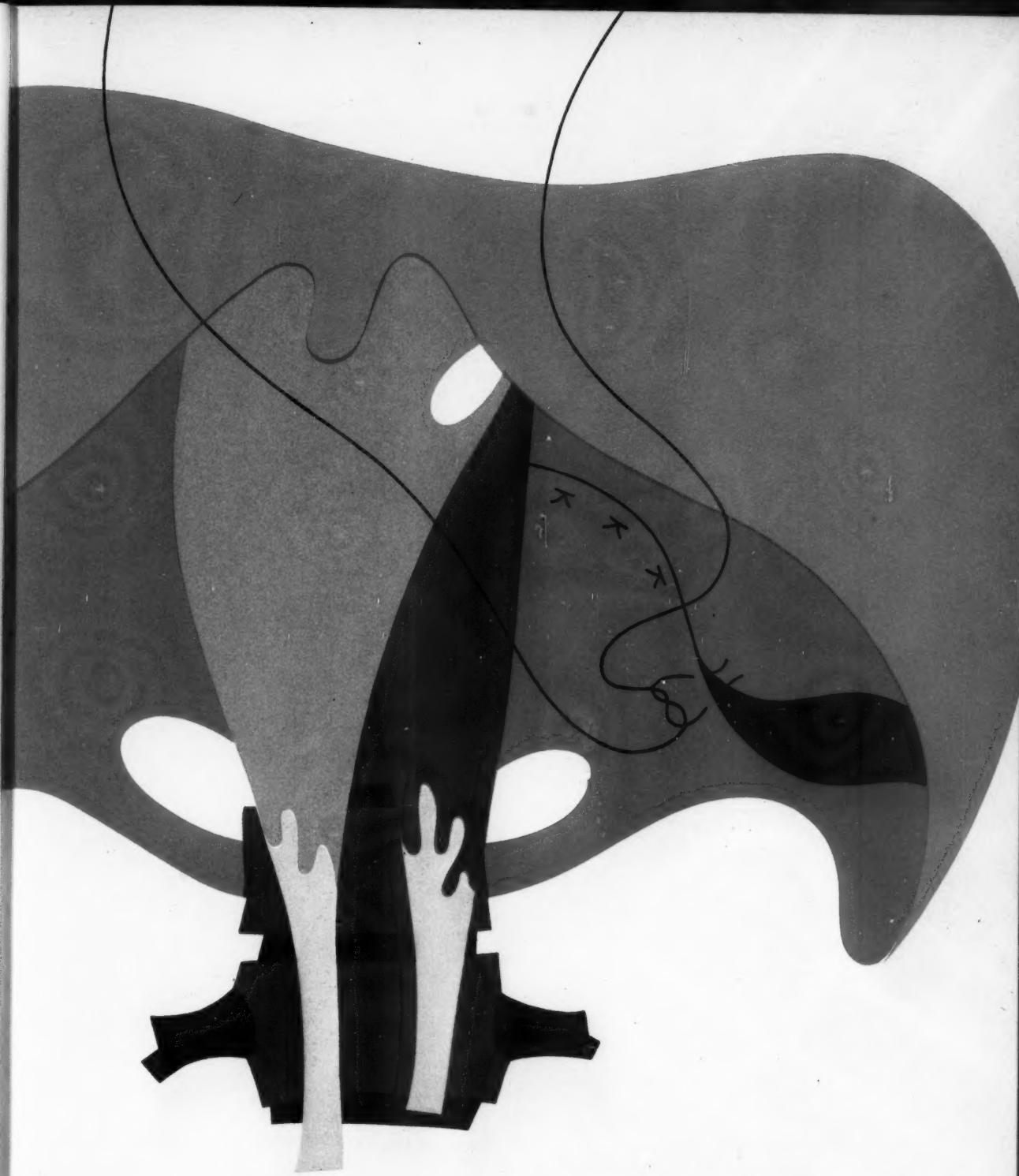
HANOVIA, WORLD LEADER IN
ULTRAVIOLET FOR HALF A CENTURY
AN ENGELHARD INDUSTRY

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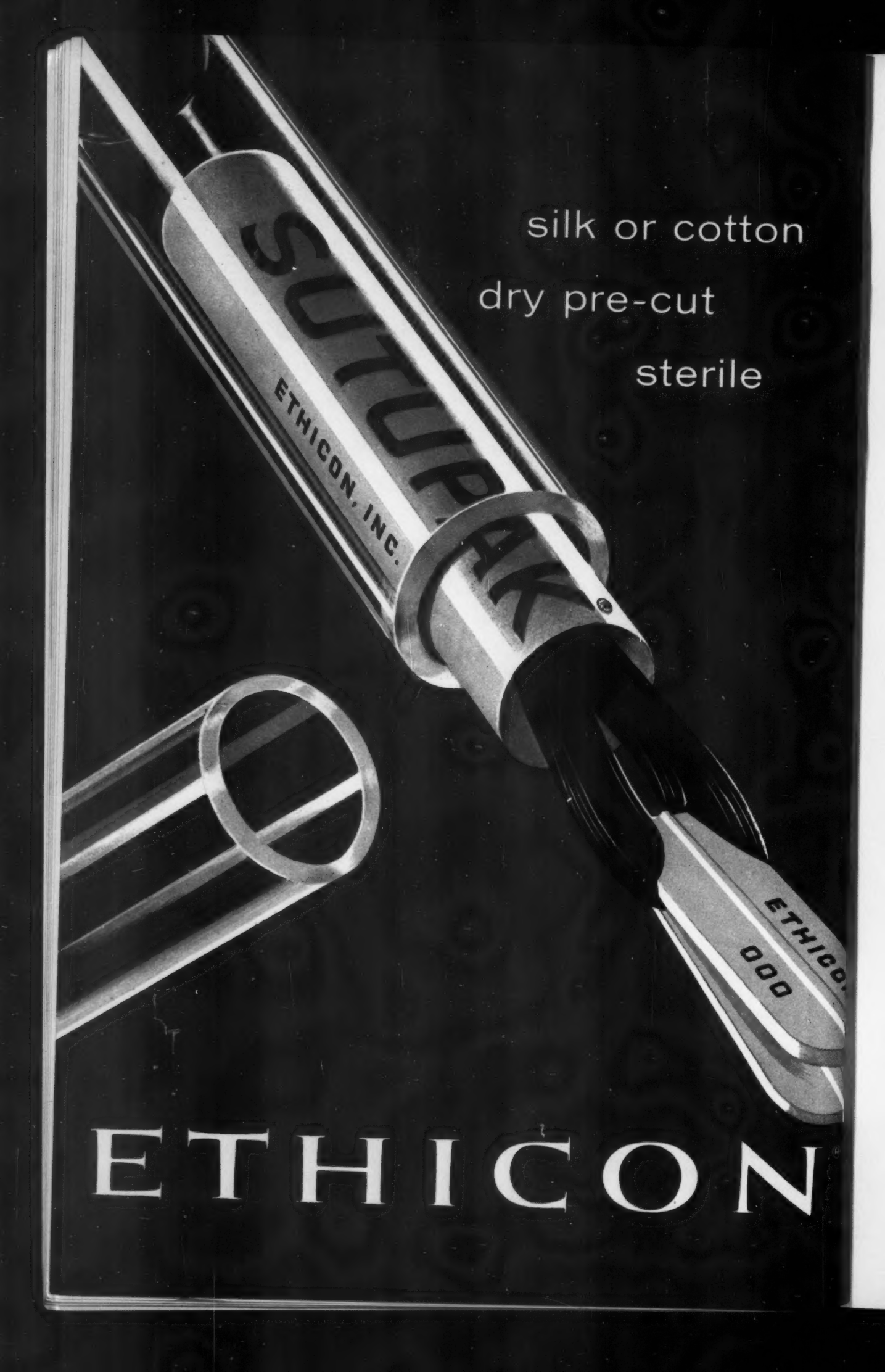
ec.



setting new standards

ETHICON®

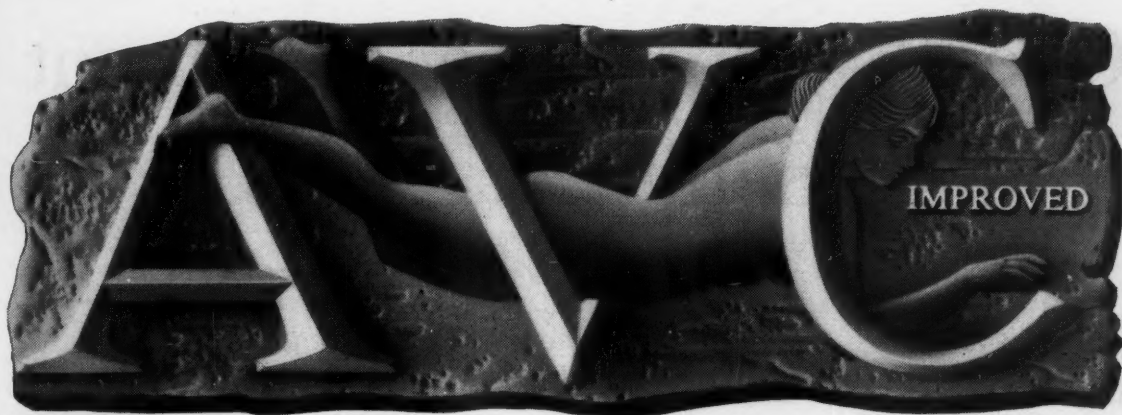
sutures



silk or cotton
dry pre-cut
sterile

ETHICON

The CLASSICAL Vaginal Therapeutic



An amazing abundance of "new" concepts in treatment are on continuous parade for one of the most vexing of all problems, the patient with the troublesome vagina. Consider the rationale of one product, AVC Improved, accepted, and in ever-expanding use these 12 years, which contains the best of these "new" ideas that have long been recognized by the medical profession.

Proved Therapeutic Efficacy

"surface-active explosive" "spreading, penetrating agent" — AVC's 9- amino-acridine provides this.

"buffered vaginal pH" — AVC's water-miscible acid carrier provides this.

"nutrient for normal vaginal flora" — AVC's lactose provides this.

"mucus digestion" — AVC's allantoin aids this action.

"pathogen killing power" "immediate relief of odor and itching" — AVC's mutually supportive allantoin-sulfanilamide-9- aminoacridine provides this.

"restoration of vaginal mucosa" — AVC's tissue-stimulating allantoin aids this.

Only AVC Improved provides all of these. Its action is basic to prevent recurrence. AVC is outstanding because it has long offered the best in vaginitis treatment. AVC Improved is supplied in 4 oz. tubes with or without an applicator.

Send for samples and reprints.

"CLINICAL ENZYMOLOGY" a film depicting a New Era in Medicine is now available for showing at medical meetings upon your request. And be sure to watch for the MED-AUDIOGRAPHS, a series of recorded clinical discussions.

PRODUCTS OF ORIGINAL RESEARCH
NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL
THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.

Local Estrogen Application Greatly Simplifies Treatment of Senile Vaginitis.

This method provides an "almost immediate healing and soothing effect" Doyle reports,¹ and "is a valuable therapeutic constituent in the management of vaginitis and vaginal infections, regardless of etiology."² This worker employed "Premarin" Vaginal Cream applied locally and found it "superior" to the use of suppositories. In addition, there was none of the "side-effects frequently noted with synthetic products . . ."¹

Favors Rapid Healing in Vaginal Surgery

In plastic vaginal surgery in the postmenopausal patient, local estrogen application prior to and after intervention will restore the atrophic and friable mucosa to a more youthful state by promoting proliferation and vascularity of the epithelium. This will facilitate the surgical procedure as well as favor more rapid healing.^{2,3}

"PREMARIN®" VAGINAL CREAM in a nonliquefying base, is standardized in terms of the weight of active, water-soluble estrogen content expressed as sodium estrone sulfate (0.625 mg. per gram). Presented in a combination package No. 874 — 1½ oz. tube with specially designed calibrated applicator; also refill available. Complete information may be obtained by writing to Ayerst Laboratories, 22 East 40th Street, New York 16, N. Y.

1. Doyle, J. C.: *California Med.* 71:15 (July) 1949. • 2. Doyle, J. C.: *Urol. & Cutan. Rev.* 55:618 (Oct.) 1951. • 3. Hamblen, E. C., in Stieglitz, E. J.: *Geriatric Medicine*, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657.



American-MacEachern

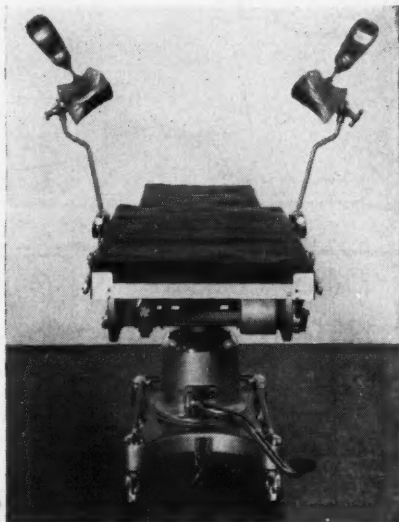
22" Operative Delivery Table.....

FOR ABDOMINAL OR PERINEAL ROUTE DELIVERY

• The new 22" 500N table assures both the patient and the Obstetrician the fullest advantages of modern obstetrical practice under all conditions.

The growing practice of performing cesarian sections in the O. B. room . . . without moving or disturbing the patient . . . is made easy by the 22" surgery width of the 500N. Yet the table will accommodate even the largest patient during normal delivery and the universally adjustable knee and foot rests accommodate all patients from the tallest to the shortest.

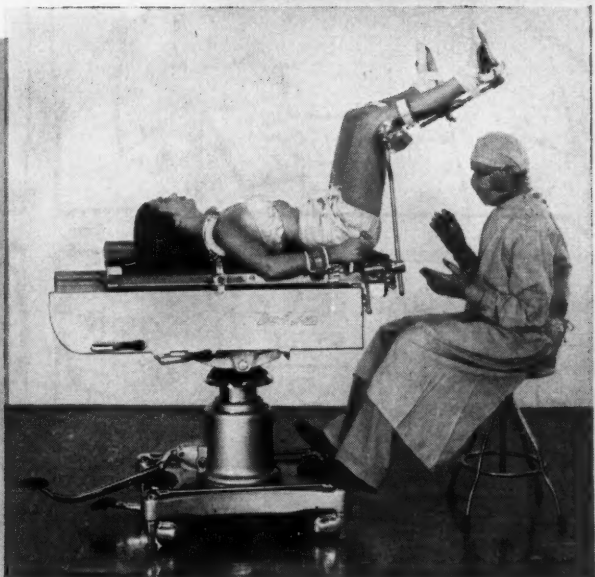
Write for bulletin C171



The "clean" lines of the 500N table provide maximum comfort and freedom for the surgeon . . . with toe space, folding handles, etc.



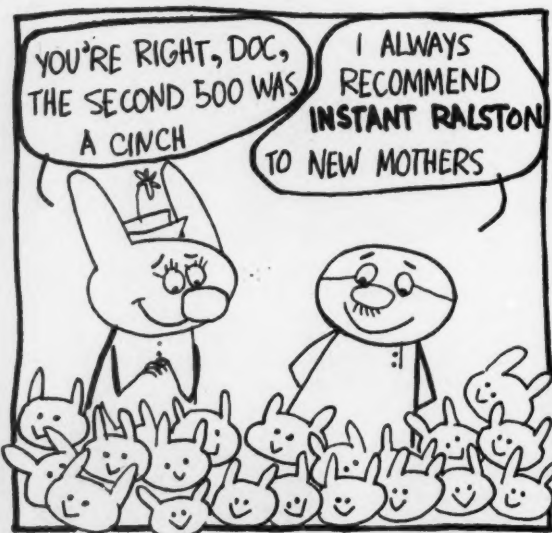
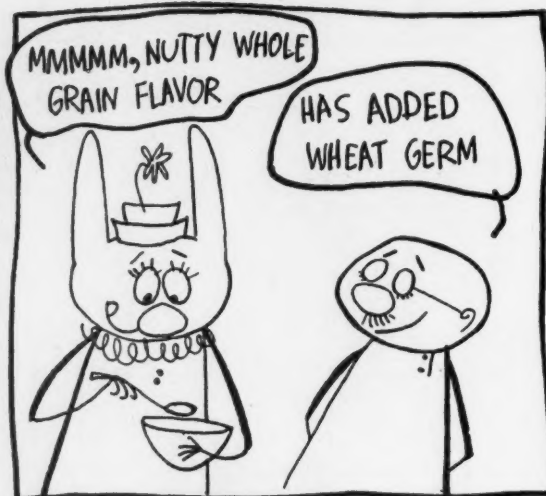
If non-elective cesarian section is indicated, patient is quickly and easily positioned for surgery simply by lowering extremities and raising the foot section. The anesthetist need not change position of head of patient.



15" height adjustment and every known obstetrical posture from high lithotomy to Walcher position provides convenient approach to the perineal field.

**AMERICAN
STERILIZER**
Erie • Pennsylvania

BRANCH OFFICES IN 14 PRINCIPAL CITIES



DOCTOR, FOR EXPECTANT MOTHERS, TOO, INSTANT RALSTON SUPPLIES EXTRA NUTRITION.

no leg cramps
with this
iron-calcium

Rarical[®] TABLETS

a unique new compound, ferrous calcium citrate, with tricalcium citrate

- iron and calcium in one molecule
- more hemoglobin in less time
- iron your patients can tolerate



CARNATION INSTANT overcomes "diet resistance" because it tastes so good!



New CRYSTAL FORM of nonfat dry milk

Only the Carnation crystal form mixes instantly even in ice-cold water...stays fresh and free-flowing on the pantry shelf. And *most* important, the flavor is *fresh*, delicious for drinking.

For the patient who prefers a richer flavor in nonfat milk, or is on restricted liquid intake, the physician may suggest an additional heaping tablespoon of crystals per glass (or an extra $\frac{1}{2}$ cup crystals per quart). This provides heavier, richer flavor—and 25% more protein, calcium and B-vitamins with no increase in fat or liquid bulk.

Top Food Award Winner



The Carnation crystals process received the biennial Food Engineering Award as the most important advance in food processing.



AVAILABLE IN
3 OR 8-QT. PACKAGE

Other Superiorities of New Carnation Instant



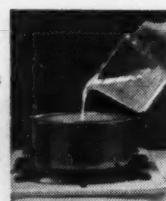
MIXES INSTANTLY

Carnation Instant crystals mix instantly with a light stir, even in ice-cold water—ready to drink.



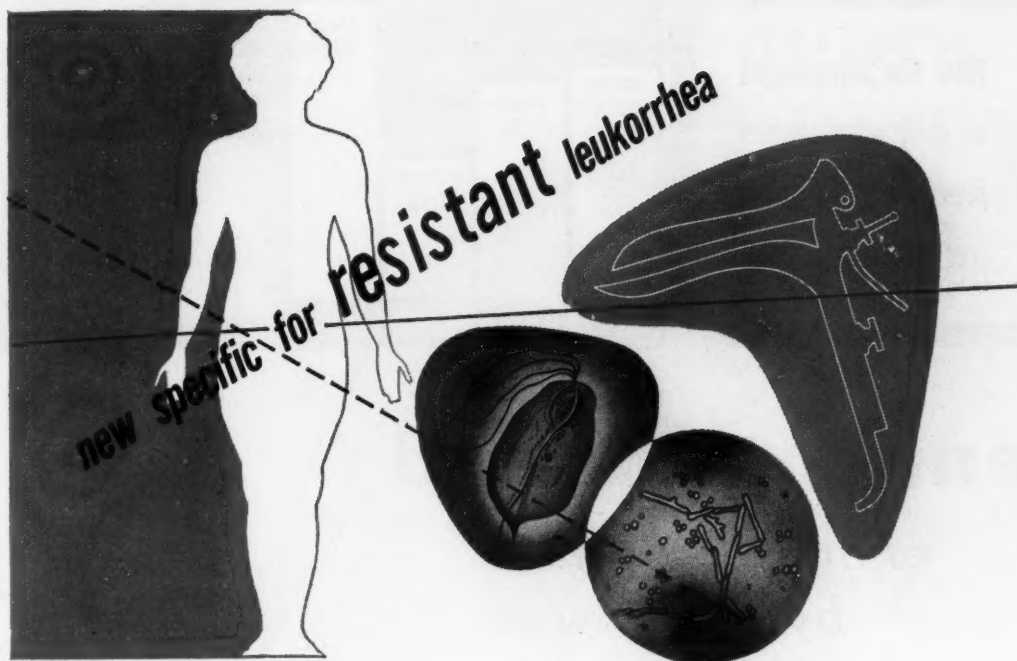
STORES ON SHELF

Carnation crystals do not harden in package. Costs up to 7¢ less per quart than bottled nonfat milk.



NO SPECIAL RECIPES

Liquid Carnation (regular or "self-enriched") is simply used in any recipe calling for milk.



HIGHLY SUCCESSFUL — Extensive clinical investigations have yielded successful results with Milibis vaginal suppositories in 97 per cent of cases of trichomonal, monilial, bacterial and mixed vaginal infections.

RAPID RESPONSE —

In many instances, 10 Milibis vaginal suppositories, one inserted every other night, proves sufficient. In some cases, however, it was necessary to extend or repeat treatment or to increase the dose up to 2 suppositories daily for two weeks.

MILIBIS[®] VAGINAL SUPPOSITORIES

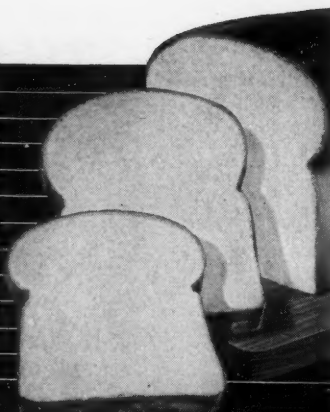
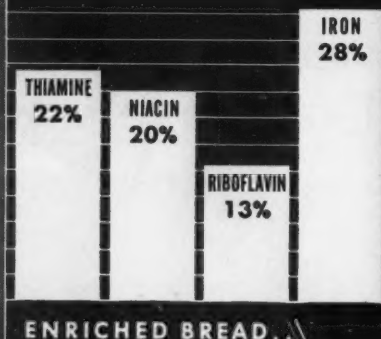
Supplied in boxes of 10, each suppository containing 0.25 Gm. of Milibis in a gelatin-glycerine base.

Winthrop

LABORATORIES • NEW YORK 18, N. Y. • WINDSOR, ONT.

Milibis, trademark reg. U. S. Pat. Off., brand of glycobiorzol

*Note the percentages
of daily allowances*
provided by six slices
of enriched bread.*



enriched bread

*endorsed again
by authorities
on public health*

ENRICHED BREAD, marketed since 1941, recently has been endorsed again by the Food and Nutrition Board of the National Research Council and by the Council on Foods and Nutrition of the American Medical Association.¹ This reaffirmation of endorsement in former years (1939, 1941, 1946) is based on "good evidence" that enriched bread has been "beneficial to the public," has "encouraged sound nutritional practices," and has contributed notably to "correcting deficiencies in the diets of the general population."

Nationally marketed enriched bread merits a large share of the credit for "the great gain in public health" in recent years, attributed to modern food commodities possessing high nutrient content. "Within the past two decades, for the first time in our history we have reached a national pattern of food practices that permits almost a complete escape from the classical forms

of nutritional deficiency diseases."² None of the diseases caused by deficiencies of thiamine, riboflavin, niacin, and iron—the nutrients with which bread is enriched—is as widespread as in former days.

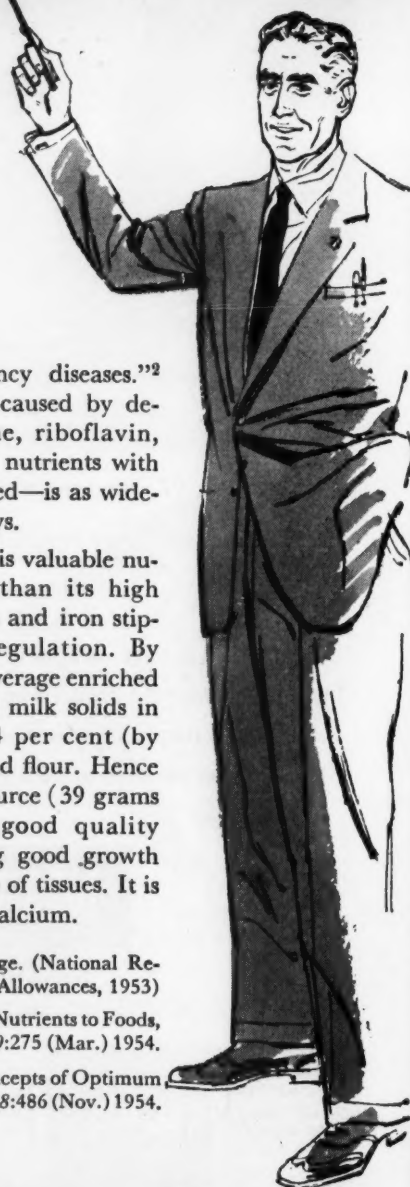
But enriched bread is valuable nutritionally for more than its high amounts of B vitamins and iron stipulated by official regulation. By commercial practice, average enriched bread contains nonfat milk solids in amounts averaging 4 per cent (by weight) of its contained flour. Hence it also represents a source (39 grams per pound loaf) of good quality protein for supporting good growth as well as maintenance of tissues. It is also a good source of calcium.

*For man 45 years of age. (National Research Council Dietary Allowances, 1953)

1. The Addition of Specific Nutrients to Foods, Public Health Reports 69:275 (Mar.) 1954.
2. King, C. G.: Newer Concepts of Optimum Nutrition, Food Technol. 8:486 (Nov.) 1954.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE, CHICAGO 6, ILL.



prophylaxis for narcotic-induced apnea



MAJOR ADVANTAGES: In therapeutic dosage, quickly boosts minute volume and respiratory rate 200 to 300 per cent; does not induce convulsions.

Nalline[®] Hydrochloride

(NALORPHINE HYDROCHLORIDE U.S.P., MERCK)

A strong case can be made for the routine administration of Nalline to all mothers in labor who have been sedated with narcotics. Administered to such patients five to fifteen minutes before delivery, Nalline causes a significant decrease in the incidence of neonatal apnea. Not only is the need for resuscitation reduced but Nalline also shortens the time for first gasp and the time for establishing respiration.

INDICATIONS: Respiratory depression and circulatory collapse due to morphine, heroin, methadone, Dromoran[®], Levo-Dromoran[®], Nisentil[®], Dilaudid[®], Pantopon[®], and Demerol[®].

SUPPLIED: In 1-cc. and 2-cc. ampuls, and 10-cc. rubber-capped vials (5 mg./cc.). Also, in 1-cc. ampuls (0.2 mg./cc.) for neonatal use. Nalline comes within the scope of the Federal Narcotic Law.



Philadelphia 1, Pa.
DIVISION OF MERCK & Co., INC.

this is premenstrual tension...

ITS CAUSES	ITS EFFECTS
<p>(a) periodic overproduction of pituitary antidiuretic hormone (ADH) leading to increased antidiuretic activity</p> <p>(b) psychogenic factors, concomitants of menstruation</p>	<p>abnormal water retention</p> <p>electrolyte imbalance</p> <p>disturbed carbohydrate metabolism (hypoglycemia)</p> <p>nervous system lability</p>
ITS SYMPTOMS	ITS EFFECTIVE TREATMENT
<p>weight gain • abdominal bloating breast tenderness</p> <p>weakness and fatigue mental dullness • depression</p> <p>vertigo • irritability anxiety • palpitation</p> <p>abdominal pain thigh pain • headache</p>	<p>PAMBROMAL</p> <p>Each tablet contains:</p> <ul style="list-style-type: none"> • Pamabrom (to neutralize the action of ADH) 50 mg. • Dextro-amphetamine sulfate (to elevate the mood) 2.5 mg. • Carbromal (to relax tension) 130 mg. • Salicylamide (to relieve pain) 250 mg.

Whittier

WHITTIER LABORATORIES • CHICAGO 11, ILLINOIS

this is **PAMBROMAL...**

a new and specific
treatment for
premenstrual tension...

1. neutralizes the antidiuretic hormone			
	Subject 1	Subject 2	Subject 3
Diuresis without pamabrom	106 cc.	275 cc.	210 cc.
Diuresis with pamabrom (100 mg.)	950 cc.	980 cc.	1200 cc.

This is how pamabrom (an ingredient of Pambromal) promotes diuresis. Subjects were given 1000 cc. of water and injected with antidiuretic hormone (pitressin). When pamabrom was administered, the water-retaining effect of the antidiuretic hormone was almost completely neutralized.

(Bickers, W., and Woods, M.: New England J. Med. 245: 453, 1951)

2. controls nervous system lability

Pambromal contains both dextro-amphetamine sulfate and carbromal, a reliable sedative. In addition to controlling fluid retention, Pambromal thus provides efficient sedative and antidepressant actions. Irritability, anxiety, and fatigue are counteracted. Tensions are relaxed and a sense of cheerful well-being is established.

3. relieves pain more effectively

Pambromal contains salicylamide, a time-tested and proven analgesic considerably more potent than other salicylates.

controls...fluid retention...anxiety-tension...pain...

PAMBROMAL[®] TABLETS

Bottles of 24 and 100.



For the well-being
of your patients

TAMPAX

intravaginal protection
during menstruation.
Three absorbencies.

TAMPAX INCORPORATED
Palmer, Massachusetts

OB-2-6





Trichomoniasis: 89.9% cure rate* in one menstrual cycle

Your patient's symptoms disappear within 72 hours with this dual regimen. The thoroughness of insufflation in the doctor's office and convenience of suppositories at home result in a high cure rate.

- 89.9% cure rate, shown in 4 clinical studies*, 108 cases, including many which were refractory to previous therapy. Results in *one menstrual cycle* plus a few days, with this dual treatment method. Few recurrences, demonstrated by repeated microscopic examinations
- *office treatment*: insufflate Tricofuron Powder twice the first week and once a week thereafter
- *home treatment*: first week—patient inserts one Tricofuron Suppository each morning and one each night at bedtime. Thereafter: one suppository a day—a second if needed—to maintain trichomonacidal action

Suppositories contain 0.25% Furoxone® (brand of furazolidone) in a water-miscible base, hermetically sealed in green foil. Box of 12. Powder contains 0.1% Furoxone in water-soluble powder base composed of lactose, dextrose, and citric acid; bottle of 30 Gm.



TRICOFURON
VAGINAL SUPPOSITORIES AND POWDER

*Personal Communication to Medical Department, Eaton Laboratories.
Detailed information available on request.

EATON LABORATORIES, Norwich, N.Y.



NITROFURANS

a new class of antimicrobials
neither antibiotics nor sulfas



NATIONAL PHENOMENON

THE PROPHETS OF DOOM who talked of the nation's dwindling population were never more wrong. Today improved economic and social conditions are resulting in bigger families — *planned* big. Families of three or more children have increased 47 per cent during the past seven years.¹ A survey just completed among 29,494 graduates of 178 colleges shows that men of the class of '45 have families averaging 70% larger than those of the class of '36 in the ten years after graduation.²

Pregnancies wanted—Women seeking advice today on conception control want to make sure that the method recommended will not impair future fertility. As a dependable method that can be counted on to permit conception *when* the patient wants to conceive, the diaphragm-jelly method is unexcelled.

Regular users of diaphragm-and-jelly discontinued the method in the hope of pregnancy, and "25 to 30 per cent achieved pregnancy within one month."³

Comfort and peace of mind—RAMSES® Diaphragm and Jelly combine comfort for the patient with confidence in the method prescribed. The flexible, cushioned rim

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*Active
RAMSES



THE PLANNED BIG FAMILY

never of the RAMSES Diaphragm assures the patient utmost comfort. Flexible in all planes, the RAMSES Diaphragm never hampers movement. RAMSES Jelly,* "a 10-hour jelly" because it occludes that long, quickly immobilizes sperm and is well tolerated.

Prescribe RAMSES protection for your young patients who want their families *when* they want them. They will learn to rely on RAMSES as physicians for more than thirty years have relied on these fine dependable products. At all pharmacies: RAMSES "Tuk-A-Way"® Kit (#701)—diaphragm, introducer and jelly in a neat zippered bag, RAMSES Diaphragms 50-95 millimeters in size, RAMSES jelly in 3 and 5 oz. tubes.

JULIUS SCHMID, INC.

423 West 55th Street, New York 19, N. Y.

1. U. S. Government figures.

2. College Study Report: Population Bulletin 11:45 (June) 1955.

3. Tietze, C., in Dickinson, R. L.: Techniques of Conception Control, ed. 3, Baltimore, Williams & Wilkins Co., 1950, pp. 55-57.

*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

RAMSES and "TUK-A-WAY" are registered trade-marks of Julius Schmid, Inc.



*New...fastest
tastiest...*

broad-spectrum

TETRABON*

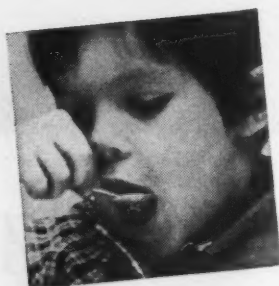
BRAND OF TETRACYCLINE

and broad-spectrum, vitamin-fortified

TETRABON SF†

BRAND OF TETRACYCLINE HYDROCHLORIDE WITH VITAMINS

homogenized mixtures



ready to use...
readily accepted...
rapidly absorbed...
(therapeutic blood levels
within one hour)...
rapidly effective...

Delicious, unusual blends
specially homogenized to
provide therapeutic blood
levels within one hour. 125
mg. tetracycline per 5 cc.
teaspoonful. Tetrabon SF
provides, in addition, the
vitamins of the B complex,
C and K recommended for
nutritional support in the
stress of infection.

*Bottles of 2 fl. oz., packaged
ready to use.*

*Trademark

†Trademark for Pfizer-originated, vitamin-
fortified antibiotics



PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N.Y.

Romilar —
a real
cough specific

A 10-mg dose of Romilar
equals a 15-mg dose
of codeine in specific
antitussive effect.

Yet Romilar® 'Roche' is
non-narcotic; it does
not cause drowsiness,
nausea or constipation.
Tablets, 10 mg; syrup,
10 mg/4 cc; expectorant,
15 mg Romilar plus
90 mg ammonium chloride
per 5 cc.

ROCHE
Original Research
in Medicine and Chemistry



Deputy Doctor —

Once she gets home from the hospital, Mother becomes your deputy in seeing that the newborn youngster gets his daily vitamin needs. And she'll find it easy if you prescribe Vi-Penta® Drops. Just 0.6 cc added to the formula daily provides the required A, C, D, and B vitamins (including B₆), and you know they're stable and potent because they're dated.

Hoffmann-La Roche Inc • Nutley • N.J.

*in hypertensive
complications
of pregnancy*

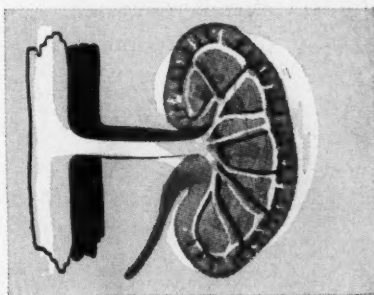
Apresoline[®]

hydrochloride
(hydralazine hydrochloride CIBA)

*may produce
dramatic results*

Within 10 to 12 minutes after the intravenous administration of a single dose of 10 to 50 mg. (average 30 mg.) of Apresoline hydrochloride, blood pressure in a group of patients with acute toxemia of pregnancy began to fall.¹ Within 30 minutes, blood pressure levels became normal and remained so for 4 to 22 hours.

In a group of patients with essential hypertension associated with pregnancy, the same intravenous dose brought about an average fall in blood pressure of 11 per cent systolic and 19 per cent diastolic.¹



SUPPLIED: Ampuls of 1 ml., containing 20 mg. per ml. Tablets, 10 mg. (yellow, double-scored), 25 mg. (blue, coated), 50 mg. (pink, coated), bottles of 100, 500 and 1000; and 100 mg. (orange, coated), bottles of 100 and 1000.

1. Assali, N. S., and Suyemoto, R.: Am. J. Obstet. & Gynec. 64:1021 (Nov.) 1952.

C I B A
Summit, N. J.

MEDICAL HORIZONS TV Monday P.M.
Sponsored by CIBA

ABC-TV

how doctors avoided 50,000,000 headaches

Until 1929, stomach-aches in babies, and other problems connected with artificial infant feeding, were a major cause of headaches for doctors.

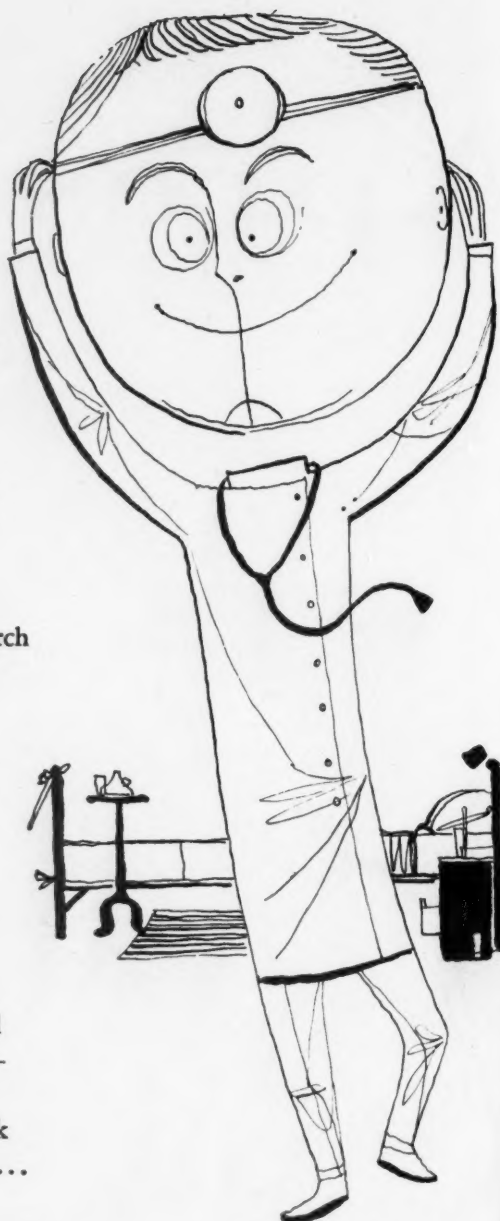
But no more. In that year, medical research determined that evaporated milk is the most satisfactory all-round solution to infant feeding problems.

Since then, more than 50,000,000 babies have made sure, steady growth on evaporated milk formulae...

preventing a feeding problem, with its attendant headache for the doctor, 50,000,000 times.

And today, evaporated milk formulae still combine *all* the most essential qualities—the higher level of protein sufficient to duplicate the growth effect of human milk... flexibility in carbohydrate adjustment... maximum nutritional advantages... and *minimum cost*.

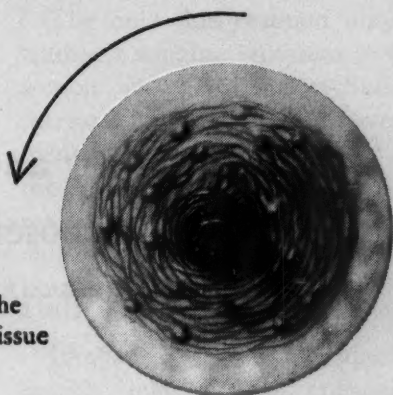
PET EVAPORATED MILK
is the "going home" formula for more babies than any other form of milk.



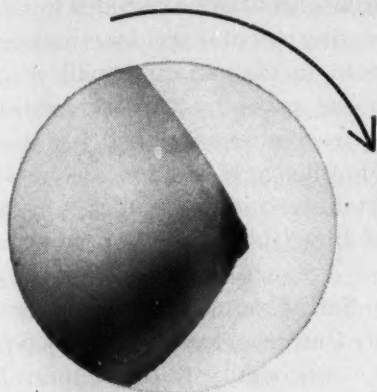
PET MILK COMPANY • ARCADE BUILDING • ST. LOUIS 1, MO.

FISSURED NIPPLE THERAPY

The use of White's Vitamin A & D Ointment soothes and softens the fissured nipple, promotes tissue regeneration.



WHITE'S VITAMIN A & D OINTMENT

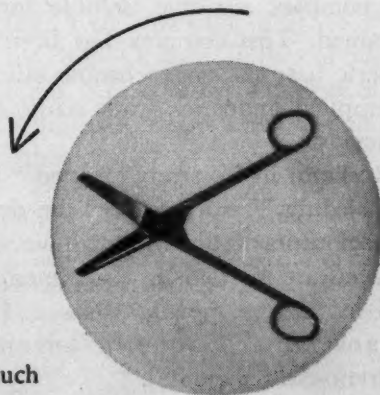


NIPPLE ROUTINE

—a valuable and simple prophylactic measure against drying, fissuring and erosion.

AFTER EPISIOTOMIES

As a post-surgical dressing, White's Vitamin A & D Ointment provides comfort for the patient and encourages rapid healing.



Specify White's Vitamin A & D Ointment also in such conditions as burns, diaper rash, chafing, indolent ulcers.

Recommend the 1½ or 4 oz. tubes; the 1 lb. or 5 lb. jars.



WHITE LABORATORIES, INC./KENILWORTH, NEW JERSEY

A Laboratory and Clinical Report on Adrenosem® Salicylate

(BRAND OF CARBAZOCHROME SALICYLATE)

History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam¹ in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"² enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. . . . One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.²⁻⁷

(* U.S. Patent 2,581,850)

Sherber, in an early study,³ concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted, and is superior to any similar material that is now available."

He continues, "From our experience it appears that adrenochromazone complex is indicated in preventing vascular accidents incident to hypertension; in maintaining small vessel integrity; in the preoperative preparation where oozing from a vascular bed is anticipated, as in tonsillectomies, adenoidectomies and prostatectomies; and as an adjunct in the treatment of bleeding from such surgical procedures."

Adrenosem Salicylate may be administered simultaneously (but separately) with any type of anesthetic, anticoagulant, or vitamin K and heparin.

A Unique Systemic Hemostat

Clinical investigators²⁻⁷ are in agreement that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeability and by promoting the retraction of severed capillary ends. It aids in maintaining normal capillary integrity by direct action on the intercellular "cement" in capillary walls. The interesting work of Fulton⁸ confirms this. Adrenosem Salicylate, since it is not a vasoconstrictor, has no effect on large severed blood vessels and arterioles.

Adrenosem Salicylate is being used both prophylactically and therapeutically in thousands of hospitals, and in virtually every type of surgical procedure. It has also proved most useful in dental surgery.⁷

Owings reported on the use of Adrenosem Salicylate in controlling postoperative adenoid bleeding in 102 cases.⁴ "We have used 2½ mg.

($\frac{1}{2}$ ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from previous records, without Adrenosem Salicylate medication.

Peele reports on the use of Adrenosem Salicylate in treating 178 patients with 24 different conditions.⁵ The drug was first used to control postoperative hemorrhage from the adenoid region. He adds: "The results were so dramatic that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagologic procedures, to treat postoperative hemorrhage from the tonsil and adenoid regions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate in controlling bleeding and oozing in 330 patients is reviewed by Bacala.⁶ "Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely benefited by this metabolic hemostat, making a diminution of the control incidence of post-tonsillectomy bleeding of 19.8% down to 7%. It has also been found useful in gastro-intestinal bleeding, cataract extraction, epistaxis, incisional seepage, trans-urethral prostatectomy, menometrorrhagias, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and prevention of capillary hemorrhages during hedulin or dicumerol therapy."

Side Effects

All investigators concur that, at recommended dosage levels, Adrenosem Salicylate is free from toxic effects. No cumulative effects

attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."⁶

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with:
tonsillectomy, adenoidectomy and nasopharynx surgery;
prostatic and bladder surgery;
uterine bleeding;
postpartum hemorrhage;
dental surgery;
chest surgery and chronic pulmonary bleeding.

Dosage

For recommended dosage schedules, please send for detailed literature.

Supplied

Ampuls: 5 mg., 1 cc. (package of 5).
Tablets: 1 mg. S.C. Orange, bottles of 50.
Tablets: 2.5 mg. S.C. Yellow, bottles of 50.
Syrup: 2.5 mg. per 5 cc. (1 tsp.), 4 ounce bottles.

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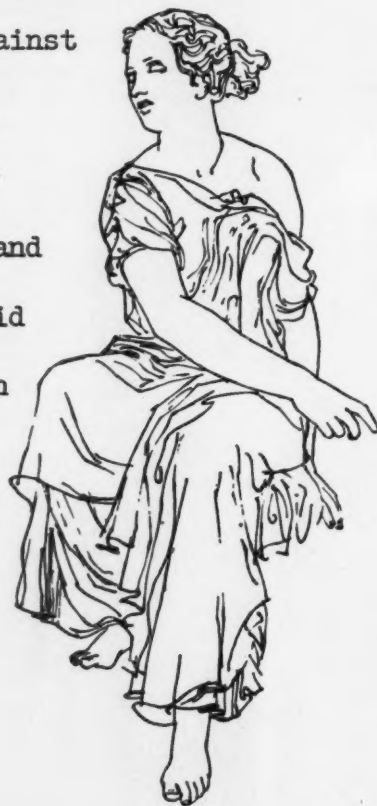
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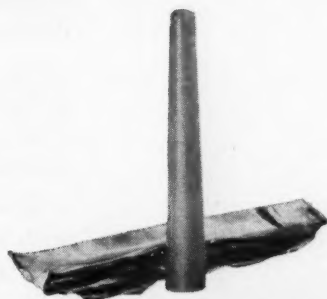
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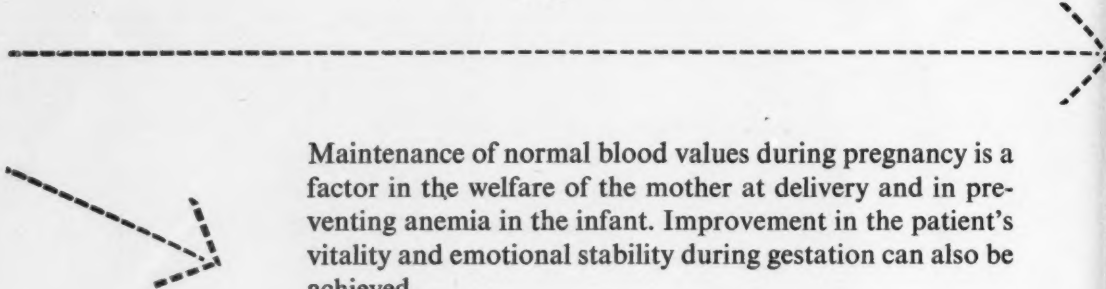


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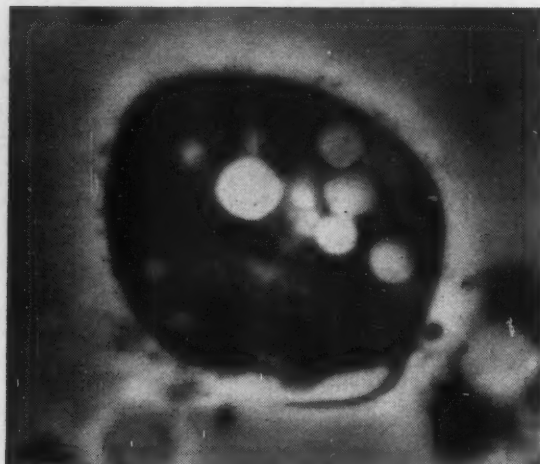
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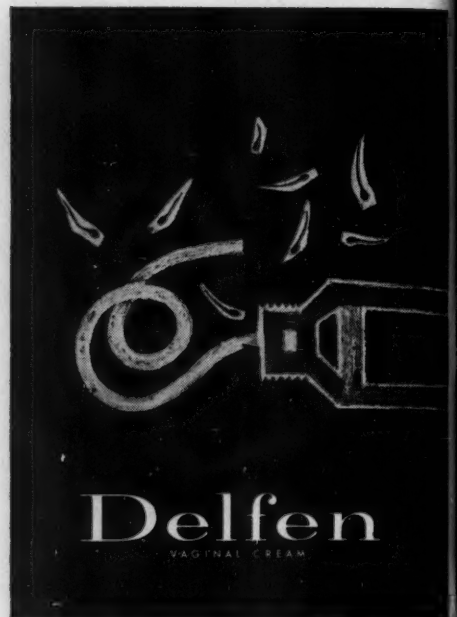
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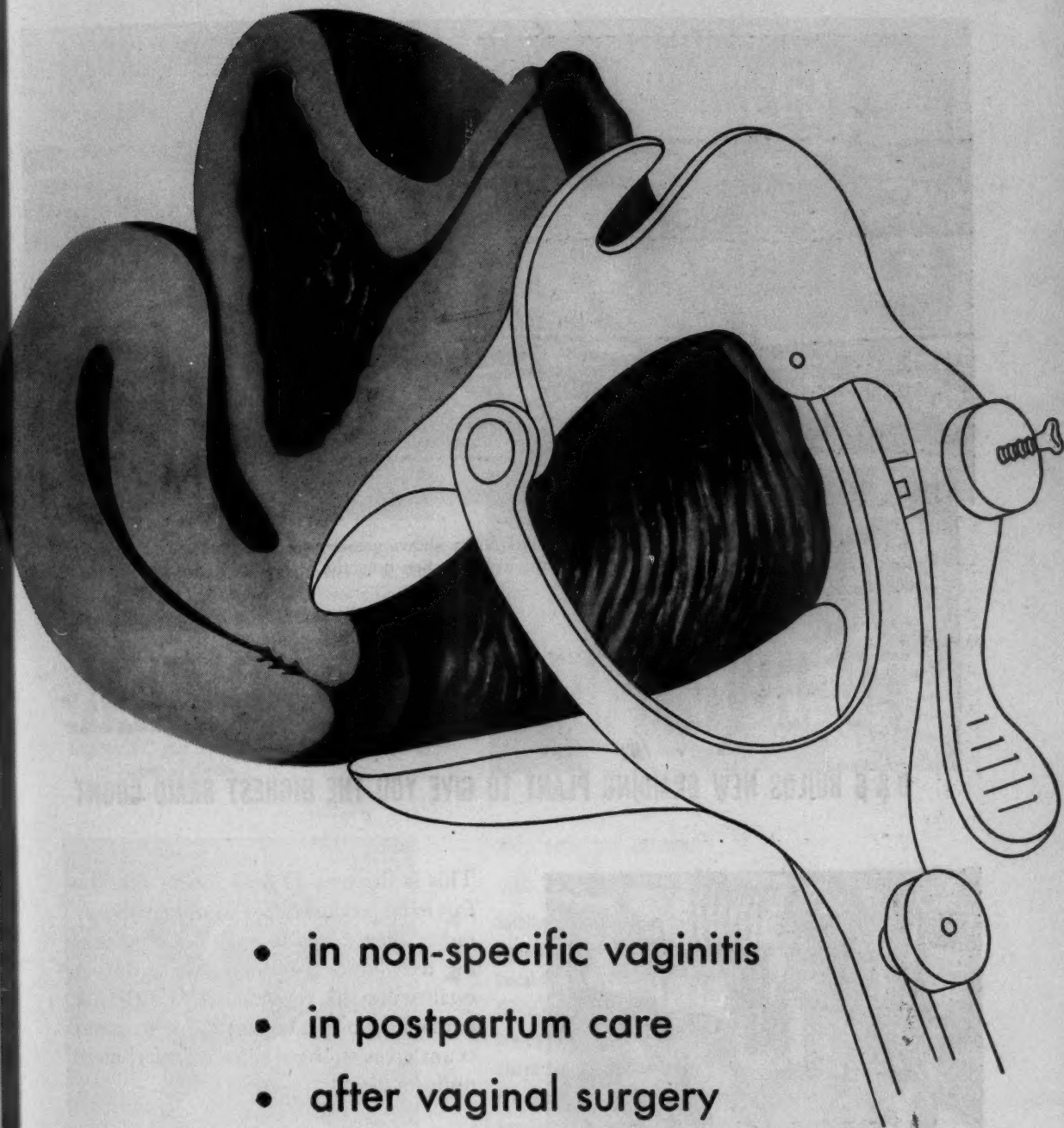
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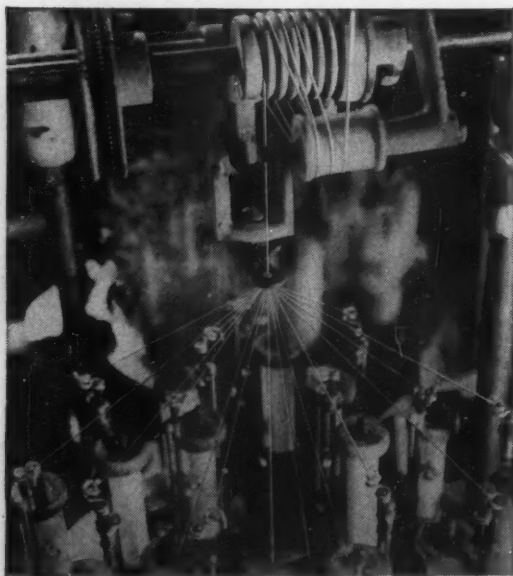




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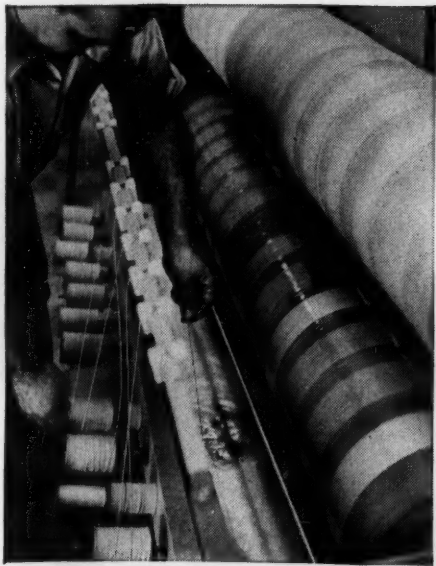
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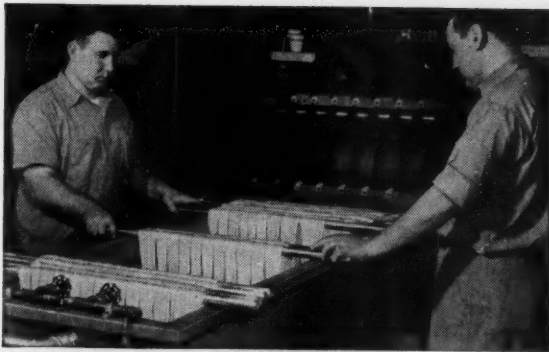
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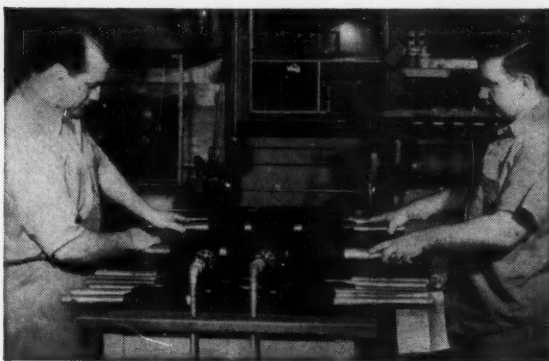


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It often happens that the physician's time and skill in clearing up vaginal trichomoniasis are wasted because the husband will re-infect the wife. Fortunately, there is a method of circumventing this endless cycle of re-infection.

Husband often the carrier. "Approximately 39 to 47 per cent of resistant cases are reinfections from the sexual partner."¹ Whittington reports infestation in the male in 27 per cent² and Freed in 28.5 per cent.³ A study of all foci of infection, such as urethra, prostate, seminal vesicles, bladder, kidneys, pelvis and preputial sac, would probably reveal even higher incidence in the male.

Danger without signals. Trichomonads in the male rarely produce symptoms to signal their presence.⁴

Prevent re-infection. Karnaky recommends in recurrent cases that the husband wear a condom during coitus for four to nine months. By the end of this time the trichomonads will usually die out.⁵ Davis states: "Use of a sheath by the husband has long been advised during the period a woman is under treatment and should be used permanently if he carries the infection."⁶

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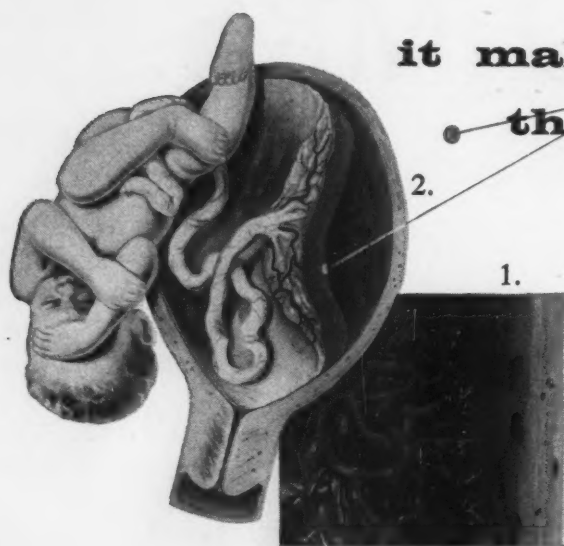
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Original Communications

HEMODYNAMIC EFFECTS OF RAUWOLFIA ALKALOID (RESERPINE) IN HUMAN PREGNANCY. RESULTS OF INTRAVENOUS ADMINISTRATION*

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California at Los Angeles)*

ALTHOUGH the root of Rauwolfia has been employed for centuries by Ayur-Vedic practitioners of India in the treatment of various central nervous disorders, its hypotensive activity was not reported until 1933. In the last five years, the use of Rauwolfia alkaloids with beneficial results in hypertensive states has been reported by numerous investigators.²⁻⁹ Several ineffective alkaloids have been isolated from Rauwolfia root,¹⁰⁻¹² but the active alkaloid reserpine was not isolated until 1952, by Mueller, Schlittler, and Bein.¹³ The chemical formula of this alkaloid is illustrated in Fig. 1. The initial pharmacologic reports on the hypotensive and central nervous depressant action of this preparation have been confirmed in both animal¹⁴ and human investigation.^{14, 15, 16} These reports indicate that reserpine probably acts on hypothalamic centers manifesting an increased parasympathetic or a decreased sympathetic response.

Following these encouraging reports in hypertensive states, this investigation was undertaken to determine the hemodynamic properties of intravenously administered reserpine in human pregnancy. The studies were designed to establish a dose-response relationship, and to determine the action of an effective hypotensive dose in normal and toxemic pregnancies.

*This investigation was supported (in part) by Grant H-1755 from the National Heart Institute, National Institutes of Health and (in part) by a grant from Ciba Pharmaceutical Products, Inc., Summit, N. J.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

Methods and Material

The clinical material consisted of 30 patients, of whom 8 were normotensive pregnant subjects and 20 were patients with toxemia of pregnancy. Two nonpregnant female subjects served for the initial plethysmographic studies. The patients were selected from the obstetric wards of the Los Angeles County and Harbor General Hospitals. The ages of the patients varied from 18 to 40 years, and the length of gestation from 28 to 40 weeks. All patients were kept at bed rest for at least 12 to 24 hours prior to the study, and the only medication administered in this preliminary period was phenobarbital in small dosage. During this period, spontaneous variations in blood pressure and pulse rate were checked and recorded every one to two hours.

On the day of study the patient was isolated in a private room, and blood pressure and pulse readings were taken every 1 to 5 minutes for a period which varied from 15 minutes to 2 hours. The averages of these readings served as controls. The purified crystalline alkaloid, reserpine,* prepared in ampules of 2.5 mg. per cubic centimeter of propylene glycol, was then administered by a single rapid intravenous injection, in doses ranging from 0.25 to 20 mg. Occasionally after the smaller doses, the same patient was given several injections of increasingly larger doses with an interval of one to two hours between injections. Further pulse and blood pressure readings were then taken every 2 minutes for the first 15 minutes and every 5 minutes thereafter until the maximum effect was observed; subsequent readings were recorded at intervals of one-half to one hour until the values returned to control levels. The three lowest blood pressure readings after the injection of reserpine were averaged to determine the "floor" or maximal hypotensive response to the drug. The mean arterial blood pressure (MBP) was obtained by adding one-third of the pulse pressure (PP) to the diastolic pressure (DP). The stroke volume (SV) and cardiac output (CO) were estimated by the formula of Starr.¹⁷

$$SV = 91 + (0.54 \times PP) - (0.57 \times DP) - (0.61 \times \text{Age})$$

$$CO = \text{Pulse} \times SV$$

The total peripheral resistance was calculated by the method of dividing the mean blood pressure by the cardiac output per second and multiplying the ratio by 1,332 in order to reduce it to the conventional unit of dynes per second per centimeter⁵.

The rate of digital blood flow was studied on 4 pregnant and 2 nonpregnant patients. Blood flow to the fingers and that to the toes were recorded simultaneously by the electronic pneumoplethysmograph described by Winsor¹⁸ after the patient had been adjusted to the procedure for at least one hour. Digital volumes were recorded before and after rapid occlusion of the venous circulation at the level of the wrists and ankles.† The occluding cuff was inflated and deflated by an automatically controlled carbon dioxide pressure system, and the pressure in the cuff was maintained at 60 mm. Hg. The arterial inflow per 4 c.c. of digit volume was calculated from the slope of the curve obtained after venous occlusion and the values extrapolated to 100 c.c. of limb volume. Two to three determinations of digit volume and digital blood flow were made in the control period and several were recorded after injection of the drug.

*This preparation, packaged as Serpasil, was supplied by Ciba Pharmaceutical Products, Inc.

†We are indebted to Dr. Wilbur A. Selle, Professor of Biophysics, School of Medicine, University of California, Los Angeles, for the use of the plethysmograph, the venous occlusion apparatus devised by Winsor and Selle, and for his assistance in carrying out these determinations.

Vasopressor reaction to cold and to the Valsalva maneuver (Valsalva "overshoot" in blood pressure) was recorded before and after reserpine injection. The cold-pressor test was performed by recording the blood pressure every twenty seconds before, during, and after immersion of the hand to the wrist in ice water for 120 seconds. Similarly the Valsalva test was accomplished by checking the blood pressure every twenty seconds before, during, and after the subject increased her intrathoracic and intra-abdominal pressure by holding her breath in and "bearing down" for 30 seconds.

Side effects of reserpine were carefully observed and recorded after each administration of the drug.

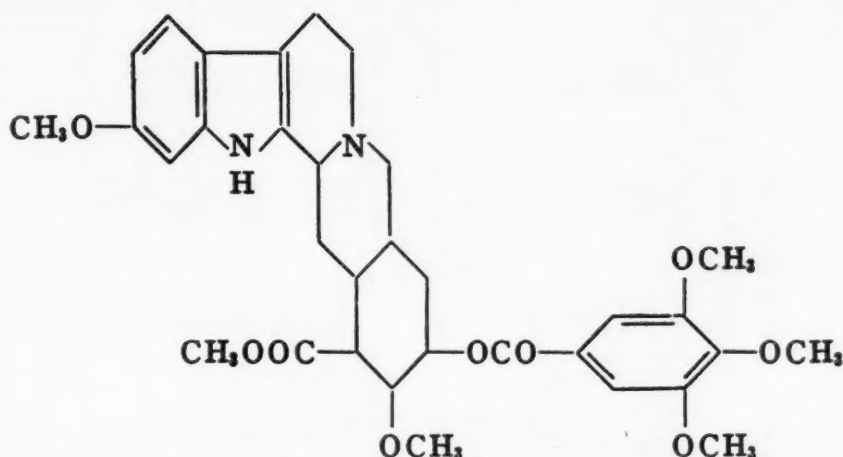


Fig. 1.—Chemical formula of reserpine (after Mueller, Schlittler, and Bein¹³).

Results

A. Effective Dose of Reserpine.—Fig. 2 shows the dose-response relationship to the intravenous administration of reserpine in normotensive and toxemic patients. It indicates that the hypotensive effect of doses below 5 mg. was negligible. With doses of 5 mg. or more, however, the hypotensive effect became more marked though the magnitude of the effect varied from patient to patient. Consequently, even though a linear relationship between the dose and hypotensive response could not be demonstrated, an effective dose was established.

In six normotensive pregnant patients, the fall in systolic and diastolic blood pressures averaged 13 and 22 per cent, respectively, following the intravenous administration of amounts greater than 5.0 mg. (Fig. 3). The same dose evoked an average drop of 24 per cent systolic and 25 per cent diastolic blood pressure in the group with toxemia.

The pattern of the vasodepressor action of reserpine was interesting. Generally, the initial effect noted by the patient after the injection of the drug was a feeling of warmth, flushing of the face, and nasal congestion. Thereafter the blood pressure began to fall gradually and the patient experienced a feeling of somnolence. In toxemic patients (Fig. 4), the maximum hypotensive effect usually occurred within two hours and persisted in lesser degree up to twelve hours thereafter. In the normotensive group (Fig. 5), both the magnitude and duration of blood pressure fall were less. A slight and variable bradycardic effect was noted in most patients in both groups after the administration of an effective dose of reserpine.

TABLE I. EFFECT OF RESERPINE IN NORMAL PREGNANCY

PATIENT	AGE	RESERPINE (MG. I. V.)	MEAN BLOOD PRESSURE		PER CENT DROP	PULSE		STROKE VOLUME (C.C.)		CARDIAC OUTPUT (L./MIN.)		TOTAL PERIPHERAL RESISTANCE	
			CONTROL	RESERPINE		CONTROL	RESERPINE	CONTROL	RESERPINE	CONTROL	RESERPINE	CONTROL	RESERPINE
A. G.	40	7.5	98	75	23.5	66	64	32.3	47.3	2.1	3.0	3,840	2,060
N. D.	20	7.5	88	79	10.2	84	82	43.0	60.8	3.6	5.0	2,015	1,450
P. C.	25	7.5	85	56	34.0	86	82	52.3	80.7	4.5	6.6	1,560	700
I. D.	24	10.0	101	78	22.7	90	88	38.1	61.9	3.4	5.4	2,452	1,192
M. B.	38	10.0	88	75	14.8	94	92	52.9	65.5	5.0	6.0	1,450	1,031
S. C.	21	20.0	77	72	6.5	84	74	62.6	62.3	5.3	4.6	1,200	1,290

TABLE II. EFFECT OF RESERPINE ON TOXEMIC PATIENTS

PATIENT	AGE	RESERPINE (MG. I. V.)	MEAN BLOOD PRESSURE		PER CENT DROP	PULSE		STROKE VOLUME (C.C.)		CARDIAC OUTPUT (L./MIN.)		TOTAL PERIPHERAL RESISTANCE	
			CONTROL	RESERPINE		CONTROL	RESERPINE	CONTROL	RESERPINE	CONTROL	RESERPINE	CONTROL	RESERPINE
A. K.	24	5.0	123	92	25.2	60	56	51.9	50.5	3.1	2.8	3,280	2,720
L. T.	27	5.0	117	99	15.4	84	76	43.5	47.3	3.7	3.6	2,610	2,260
E. F.	33	5.0	120	88	26.6	98	90	31.0	41.8	3.0	3.8	3,300	1,910
A. G.	24	6.0	125	113	9.6	90	88	54.1	51.1	4.9	4.5	2,105	2,070
E. S.	31	7.5	122	84	31.2	82	78	38.2	54.2	3.1	4.2	3,240	1,650
A. C.	19	7.5	134	87	35.0	64	70	55.2	63.7	3.5	4.5	3,160	1,590
D. C.	19	7.5	133	80	40.0	110	80	30.4	55.3	3.3	4.4	3,290	1,500
M. W.	18	7.5	125	102	19.0	96	102	43.8	57.1	4.2	5.8	2,457	1,451
M. P.	20	10.0	135	109	19.3	66	72	42.3	53.0	2.8	3.8	3,990	2,339
H. H.	36	10.0	150	108	28.0	72	64	26.4	35.6	1.9	2.3	6,540	3,880
L. M.	33	10.0	122	100	18.0	72	80	26.5	40.8	1.9	3.3	5,300	2,500
C. S.	24	10.0	137	115	16.0	92	75	33.9	37.8	3.1	2.9	3,645	3,275

B. Effect on Cardiac Output and Peripheral Resistance.—In Table I are listed the effects of reserpine on the cardiac output and peripheral resistance of normotensive pregnant patients who received doses of 5 mg. or more. At the point of maximum blood pressure reduction, the stroke volume and cardiac output were increased in 5 of the 6 normotensive patients with a concomitant decrease in total peripheral resistance. It is interesting to note, however, that Patient S. C., who exhibited a decrease in cardiac output, received the largest dose of reserpine (20 mg. intravenously).

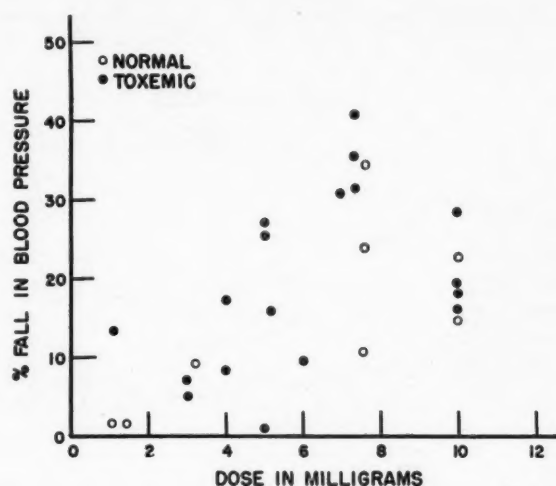


Fig. 2.—Dose-response relationship of the intravenous administration of reserpine in normotensive and toxemic patients.

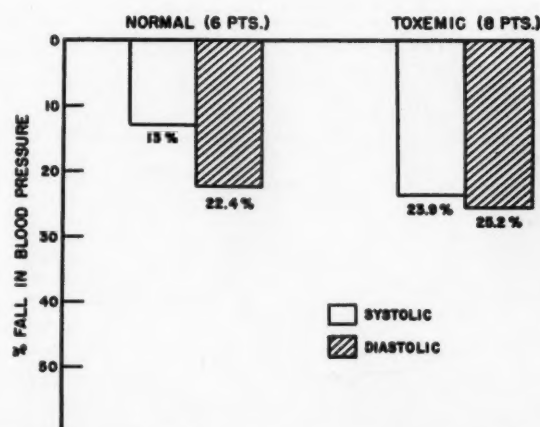


Fig. 3.—Blood pressure fall following intravenous administration of reserpine.

Of the 12 toxemic patients who received doses of reserpine higher than 5 mg. (Table II), 8 showed an increase in cardiac output concomitant with a marked reduction in the total peripheral resistance. The remaining 4 patients exhibited a moderate decrease in cardiac output, but the total peripheral resistance was reduced in *all* cases. The decrease in total peripheral resistance ranged as high as 54 per cent (Patient D. C.).

C. Effect on Peripheral Blood Flow.—The digital volume and digital blood flow increased significantly after the administration of reserpine (Table

III). The increase was progressive beginning fifteen minutes after the injection and reaching a maximum increase within two hours. These changes were evident in both the upper and lower extremities and did not show a definite relationship to the changes in blood pressure. Fig. 6 illustrates a plethysmographic recording of the fingers before and after reserpine administration indicating the increase in digital volume. Fig. 7 illustrates the tracings indicating blood flow to the lower extremities on the same patient. Note that the effect is more marked in the upper extremities.

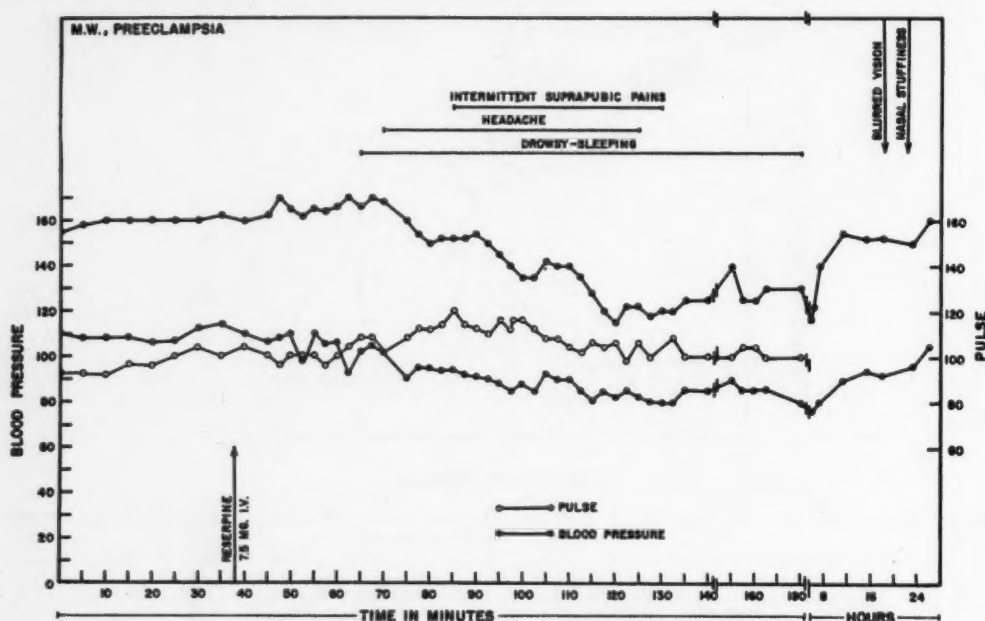


Fig. 4.—Effect of single intravenous dose of reserpine in a pre-eclamptic patient.

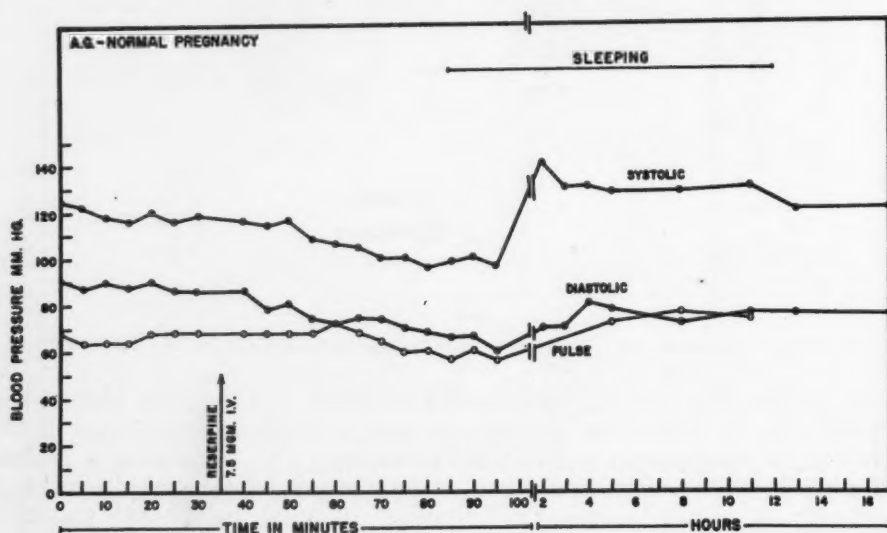


Fig. 5.—Effect of single intravenous dose of reserpine in normotensive pregnant patient.

D. Effect on Vasopressor Reflexes.—Reserpine produced no modification of the general response of blood pressure to cold (Fig. 8). Similarly the

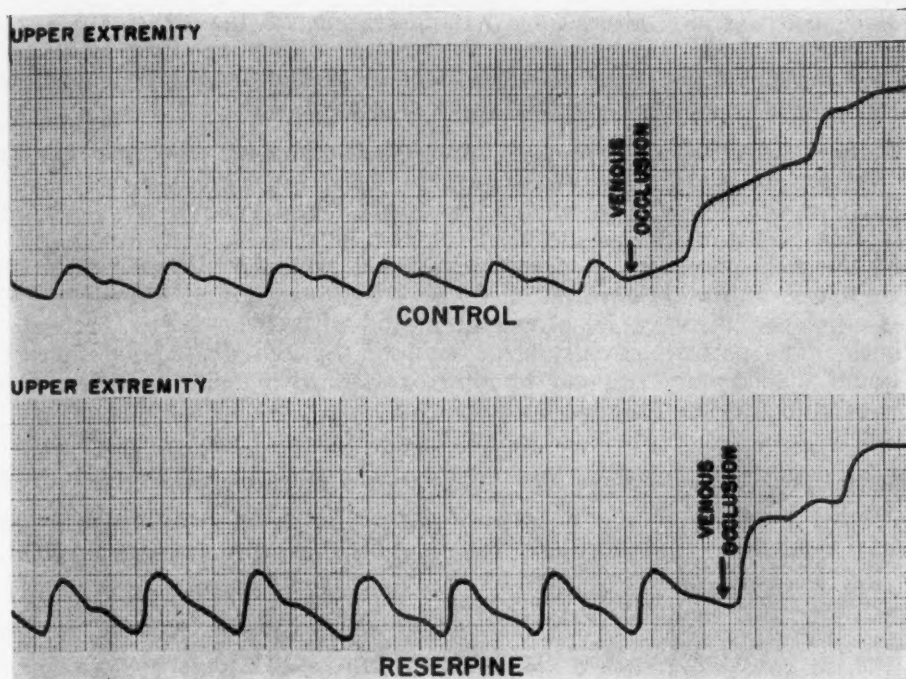


Fig. 6.—Plethysmographic recording of upper extremity before (above) and after (below) intravenous administration of 7.5 mg. reserpine. Note the higher amplitude of excursion following administration of reserpine, indicating an increase in limb volume. The increased amplitude persists after venous occlusion (indicated by rise in limb volume).

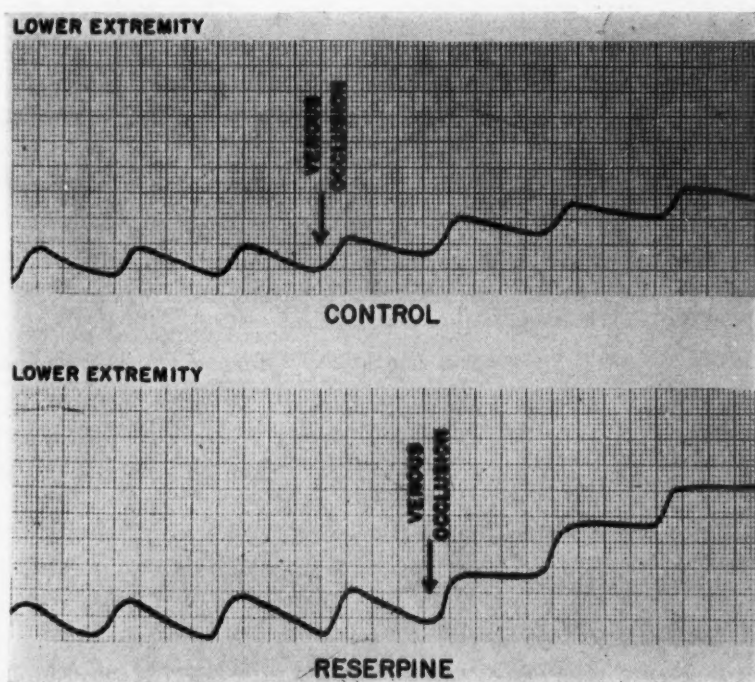


Fig. 7.—Plethysmographic recording of lower extremity in the same patient as illustrated in Fig. 6. Note that the increase in peripheral blood flow (amplitude of excursion) is relatively less than in the upper extremity.

Valsalva test was not altered by administration of the drug. Also, since postural hypotension did not occur during the maximum effect of reserpine, it is assumed that the reflexes which control the return of venous blood to the heart were not altered with the doses employed.

E. Side Effects of Reserpine.—Untoward reactions have been few, and they were not serious in the dose range tested. They included nausea, heartburn, nasal mucus congestion, flushing and warmth, dizziness, and uterine contractions. Nasal congestion was the most common side effect, and although it also seemed the most persistent, it presented no real problem. Uterine contractions occurred in 8 of the 30 cases studied, were not severe, and quickly subsided. The somnolence resulted in a restful sleep, with the patient arousable at all times. The patients usually slept soundly through disturbing distractions but would immediately respond to interrogation with no sign of mental confusion or difficulty in physical coordination.

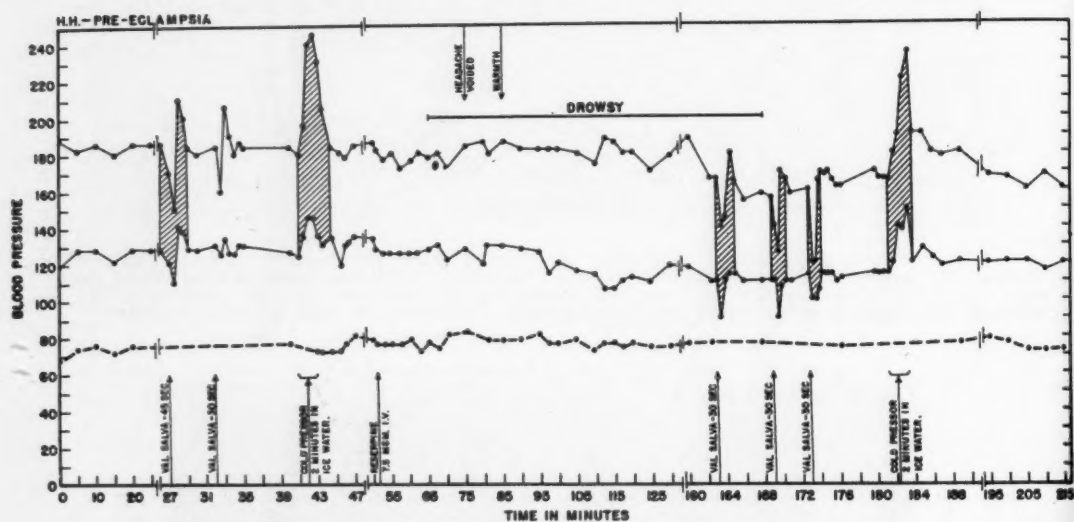


Fig. 8.—Effect of reserpine on the vasopressor reflexes in pre-eclamptic patient. Note that the cold pressor test and the Valsalva responses are not affected.

TABLE III. EFFECT OF RESERPINE ON PERIPHERAL BLOOD FLOW

CASE NO.	TYPE PATIENT	BLOOD PRESSURE (MM. HG)		BLOOD FLOW C.C./MINUTE/100 C.C. OF LIMB			
				TOES		FINGERS	
				BEFORE INJECTION	MAXIMUM CHANGE AFTER INJECTION	BEFORE INJECTION	MAXIMUM CHANGE AFTER INJECTION
1	Normal non-pregnant	108/65	106/58	2.8	12.4	4.2	22.2
2	Normal non-pregnant	108/62	100/55	3.2	10.3	3.8	16.5
3	Normal pregnant	110/70	90/62	2.3	11.4	4.1	15.7
4	Normal pregnant	108/68	100/58	2.6	10.8	3.7	16.6
5	Normal pregnant	112/70	96/57	2.5	11.7	3.3	14.2
6	Toxemia	170/110	140/90	2.2	10.6	2.8	13.2

Comment

In man, the oral administration of reserpine appears to evoke a mild hypotensive and sedative effect which becomes evident only after 5 to 10 days of continuous treatment.¹⁹ Isolated observations⁷ on the intravenous administration of reserpine to normotensive and hypertensive nonpregnant patients indicate that a gradual fall in blood pressure occurs after a 3 to 4 mg. dose. The pressor reflexes, cardiac output and renal hemodynamics have not been reported as significantly altered.

The present data obtained from study of pregnant patients with and without hypertension indicate that the effective single intravenous dose of reserpine lies between 5 and 10 mg., which is slightly higher than that reported for essential hypertension. Although the effective dose ranged between 5 and 10 mg., higher doses were tolerated without difficulty.

From analysis of the data presented, it is apparent that, since reserpine does not significantly alter the cardiac output, the major action of reserpine in producing a fall of blood pressure is by reducing peripheral resistance. Indeed, the decrease in peripheral resistance constituted the most marked and most consistent effect of administration of reserpine in our series. It is noteworthy that the increased blood flow (and, presumably, decreased peripheral resistance) is more marked in the upper than in the lower extremities. This observation is consistent with similar findings with other hypotensive drugs (Apresoline) which act centrally.²⁰ Drugs which decrease vascular resistance by a blockade of the autonomic vasoconstrictor tone (hexamethonium, Arfonad, etc.) have a more marked effect on the lower extremities, which would logically require greater intrinsic control of vasomotor tone to combat the effects of gravity.²¹ The additional significant effect of mild sedation which often gave the patients a sense of well-being must also be considered important. Such factors would favor the use of intravenous reserpine in the management of acute hypertensive toxemia of pregnancy. The usual latent period (1 to 2 hours) before obtaining the maximum response, however, speaks against its use in the acute crisis of eclampsia or severe pre-eclampsia. Consequently, these data would indicate that reserpine might best be reserved for the treatment of the toxemic episode after the acute phase has been controlled by more rapidly acting drugs.

Exact comparisons between drugs are impossible to make because of their mutual effect when used on the same patient. It was noted, however, in some cases where veratrum or Apresoline was used before or after reserpine that the hypotensive action of reserpine was less marked than that of the other drugs. In other cases, however, reserpine proved a much more effective hypotensive agent than Apresoline. Such comparisons must be made on a far larger series of patients before any conclusions can be ventured.

Untoward side effects encountered with reserpine were not bothersome, and the headache so painfully persistent with Apresoline was singularly absent. Of special interest is the onset of uterine contractions observed fleetingly in 8 patients. This action which accounts for the use of Rauwolfia root as an

ecbolic agent was in no case severe enough to constitute a contraindication to the use of the drug. The mechanism of this action, however, as well as the site of action of the drug, deserves further study.

Summary and Conclusions

1. The hemodynamic effects of intravenously administered reserpine were studied in 2 normotensive nonpregnant subjects, 8 normotensive pregnant patients, and 20 patients with hypertensive toxemia of pregnancy.

2. The optimal effective dose of reserpine was found to vary from 5 to 10 mg.

3. The maximum hypotensive effect usually occurred within one to two hours after administration of the drug. The duration of effect was variable, lasting longer with toxemic patients, and covering a period of from three to twenty-four hours.

4. The major factor associated with the lowering of blood pressure was observed to be a marked decrease in total peripheral resistance.

5. The peripheral blood flow in both upper and lower extremities was significantly increased after reserpine administration.

6. Reserpine failed to block the vasopressor reaction to cold, and did not affect the Valsalva "overshoot." Postural hypotension did not occur with administration of reserpine.

7. The hemodynamic properties of reserpine indicate that it may serve as an adjunct in the management of hypertensive toxemia of pregnancy.

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PROTOVERATRINE IN THE TREATMENT OF TOXEMIA OF PREGNANCY

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SINCE July, 1953, when Puroverine* was first made available to us we have used this drug for the treatment of the characteristic vasospasm of toxemia of pregnancy.¹ The protoveratrine used is a pure crystallized alkaloid of *Veratrum album* composed of $\frac{2}{3}$ protoveratrine A and $\frac{1}{3}$ protoveratrine B. Its major pharmacologic actions have been investigated and delineated as follows:

1. Vasodepressor Action.—

a. The main component of this blood pressure lowering action is due to vasodilation (decreased peripheral resistance) demonstrable with the plethysmograph. It is reflex in nature (von Bezold reflex) with the receptors of the afferent arc primarily in the left ventricle and impulses travel to cerebral circulatory regulating centers via fibers in the vagus nerve. The efferent arc apparently follows autonomic ganglionic pathways since the depressor action can be blocked by tetraethylammonium compounds.²⁻⁸

b. There is some evidence for a central effect.^{9, 10}

2. Cardiodecelerator Action.—

This too appears to be a reflex action with the afferent arc as stated above. The efferent arc can be blocked by atropine or by severing the vagus nerve and is therefore considered to be vagal. If pronounced, it can augment the hypotensive effect apparently by decreased cardiac output.^{2, 4, 8}

3. Vasopressor and Cardioaccelerator Action.—

This action is apparent only with large doses in experimental animals, and it seems to be due to the release of epinephrine.^{2, 9} Thus far it has not been reported in human studies.

In addition a cardiotonic effect similar, and perhaps additive, to the cardiac glucosides has been noted, as well as a diminution of glomerular filtration with transitory oliguria.⁹

Material and Methods

During the period covered by this paper there were 119 admissions, or 109 patients studied. All were hypertensive patients in whom a diagnosis of toxemia of pregnancy had been made. Further breakdown shows that of the cases treated 100 had pre-eclampsia, 6 had eclampsia, and 13 had pre-eclampsia superimposed on essential hypertension. Of these patients there were 64 admitted with albuminuria; 67 admitted with edema; and 39 with edema and albuminuria in addition to hypertension.

In order properly to evaluate the drug under study no other medication was given to patients with toxemia except magnesium sulfate. No patients

*Protoveratrine, generously supplied by Sandoz Pharmaceuticals.

with postdelivery toxemia or intrapartum fetal death on admission are included. Intrapartum analgesics were for the most part omitted or kept to a minimum for this study; however, in some cases Demerol-scopolamine or Nisentil-scopolamine combinations were used. The maximum dose of Demerol in any one patient was 200 mg. and the maximum dose of Nisentil was 80 mg.

To aid in diagnosis and treatment the following laboratory procedures were done routinely: urinalysis on admission and daily, blood type and hemoglobin determinations, blood urea nitrogen, uric acid, and serum protein level determinations. In addition routine electrocardiograms, chest x-rays, and fundoscopic examination were done. Blood pressure, pulse, and fetal heart tones were taken at intervals of one hour or less. All patients were placed in bed immediately after admission on a salt-free high-protein diet, and fluid intake and output carefully recorded. Fluid intake was limited for the first few days to output plus insensible loss.

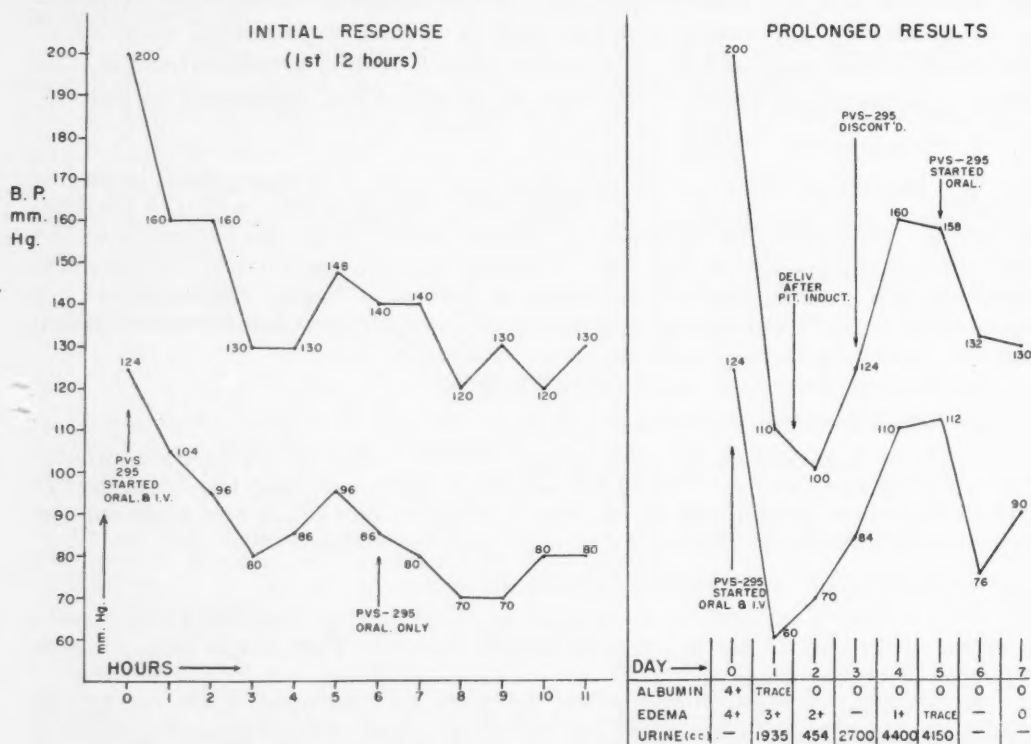


Fig. 1.—Pre-eclampsia. These graphs show the immediate and over-all response in Patient A. C. who received Puroverine, 0.2 mg. intravenously in 1,000 c.c. of 5 per cent dextrose in water on admission, and 1.0 mg. orally every four hours. Pitocin induction approximately 24 hours after control was successful and delivery uneventful. Protoveratrine was discontinued on the third postpartum day, but had to be reinstituted on the fifth postpartum day to control still significant hypertension.

The patients with mild pre-eclampsia were given only basal medication which consisted of oral doses of protoveratrine. A dose of 0.5 to 1 mg. was given every two to four hours until blood pressure fell to desired levels and then regulated according to the individual response at the dose necessary to maintain normotensive levels. Protoveratrine is potent orally and individualization of each patient's medication is important, for a marked hypotension may occur. The usual maintenance dose was 0.5 mg. every four hours.

Patients with severe pre-eclampsia and eclampsia were also given the basic medication just described and, in addition, on admission received 0.1 to 0.5 mg.

protoveratrine intravenously in 1,000 c.c. of 5 per cent dextrose in water at a rate of 30 drops per minute. If the blood pressure was not falling to a desired level within 30 minutes the rate of the infusion was increased. If within another 30 minutes the blood pressure was not responding, 1 ampule (0.1 mg.) of protoveratrine was given slowly over a period of two minutes directly into the infusion tubing. This acute injection was repeated as often as necessary to maintain blood pressure at approximately 140 systolic and/or 90 diastolic.

Since the disease may progress to intrauterine fetal death even though the usual manifestations (hypertension, edema, and albuminuria) are controlled¹¹ we feel that emptying the uterus at as early a time as compatible with good clinical judgment is an essential aspect of treatment. Accordingly, when it was felt that delivery was indicated as evidenced by difficulty of control, persistent albuminuria, or increasing levels of blood urea nitrogen and uric acid, induction was attempted for vaginal delivery whenever feasible. If at attempted induction (stripping membranes, amniotomy, and/or intravenous Pitocin) the cervix was found to be long and uneffaced, cesarean section under local or spinal anesthesia was done. Anesthesia for vaginal deliveries was pudendal block or ethylene-oxygen mixture, although we feel that saddle block could have been used.

Therefore, all patients were on the following routine:

1. Absolute bed rest
2. Routine laboratory tests
3. Fluids orally and intravenously amounting to output plus insensible loss
4. Salt-free, high-protein diet
5. Protoveratrine
 - a. Basal medication, 0.5 to 1 mg. orally every two to four hours until desired response, then as indicated for maintenance (usually only medication required in mild pre-eclampsia)
 - b. Intravenous medication, 0.1 to 0.5 mg. in 1,000 c.c. 5 per cent dextrose in water dripping at 30 to 50 drops per minute. If there is no significant response, 1 ampule (0.1 mg.) directly into infusion tubing taking two minutes for the injection and repeated as necessary
6. Magnesium sulfate, 2 c.c. 50 per cent every two hours, 4 times as indicated
7. Diuretics as necessary
8. Evacuation of the uterus as indicated by clinical course if labor has not begun during control period

Results

Blood Pressure.—In the 100 cases of pre-eclampsia blood pressure fell to normotensive or at least therapeutic levels (fall in severe pre-eclampsia and eclampsia to a systolic pressure of 160 mm. Hg or lower and/or diastolic pressure to 100 mm. Hg or lower) in all but 3 patients before delivery. In 19 the blood pressure fell to these levels in one hour, in 12 in two hours, in 8 in four hours, in 6 in eight hours, in 43 in twenty-four hours, while in 9 it took longer than twenty-four hours for control to be established. In 2 patients the blood pressure responded but was not maintained at control levels and in one patient it was uncontrollable. In general it may be seen from Table I that the response was much more rapid when intravenous medication was used. Intramuscular medication is not recommended because of its irregular absorption from edematous subcutaneous tissues.

Of the 6 patients with eclampsia, blood pressure fell to normotensive or therapeutic levels in 4 before delivery. In one it fell to these levels in one hour, in 2 in two hours, and in one in four hours. One additional patient's blood pressure responded to the drug but she had a convulsion during therapy and another patient showed no response and section was required.

Patients with hypertension and superimposed pre-eclampsia responded as follows: In 4 the blood pressure was at therapeutic levels in one hour, in 2 in two hours, in one in four hours, and in 2 in eight hours. It took twenty-four hours for one patient's blood pressure to be controlled and longer than twenty-four hours for 3 others. No patient in this small group failed to respond.

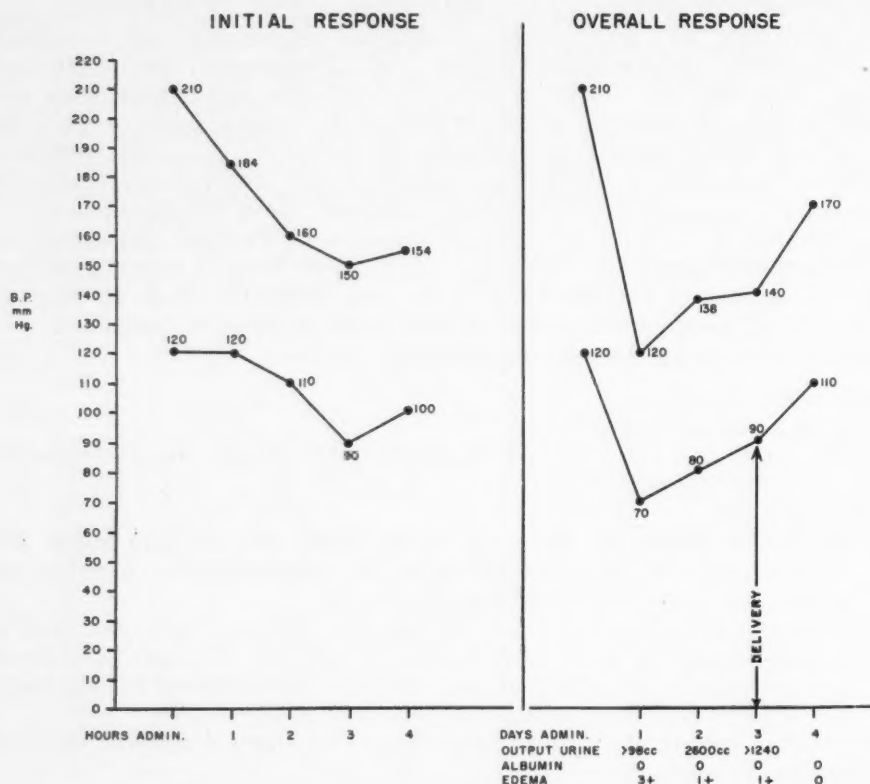


Fig. 2.—Hypertension and superimposed pre-eclampsia. Initial and over-all response in Patient B. J. who was given 1 mg. of Puroverine every 4 hours orally and 0.2 mg. in 1,000 c.c. 5 per cent dextrose in water intravenously on admission. Labor began spontaneously after an enema on the third day and delivery with pudendal block of a 2,240 gram infant was uneventful. During the first day of the puerperium the blood pressure rose in spite of treatment and the patient was discharged 7 days after delivery with an elevated blood pressure that necessitated further clinic treatment.

Proteinuria.—Of all those studied, 64 patients had proteinuria on admission, but there was information allowing breakdown on only 43 of these: 14 became protein free in twenty-four hours, 4 additional in forty-eight hours, 2 more in seventy-two hours and 12 took longer than seventy-two hours to become protein free. The remaining 11 were delivered while they still had some degree of albuminuria (Table II).

Edema.—Of 119 admissions studied 67 patients were edematous on admission and 40 of these records were susceptible to the following breakdown: 6 had no edema in twenty-four hours, 6 more in forty-eight, 4 additional in seventy-two, and 15 took longer than seventy-two hours to become edema free. In addition 9 delivered before edema had completely subsided (Table II).

Urinary Output.—No oliguria could be demonstrated twenty-four hours after admission.

Toxic Manifestations.—The most common was vomiting. Thirty-two had at least one episode of vomiting while protoveratrine was being given but in not all cases was the emesis due to the drug studied. In only 4 instances was it severe enough to necessitate decreasing the amount of protoveratrine given.

Bradycardia was observed in 16 cases and was uniformly abolished by $\frac{1}{150}$ grain of atropine.

Hypotension was present in 4 cases and could be relieved by decreasing the amount of protoveratrine given or by one of the sympathomimetic drugs such as epinephrine, ephedrine, or Levophed.

TABLE I.

TIME NECESSARY FOR CONTROL

Preeclampsia Protoveratrine	1hr.	2hrs.	4hrs.	8hrs.	24hrs.	>24	B.P. response only	uncontrolled
Intraven. & Oral	16	5	3	1	6	2		
Oral only	3	7	5	5	37	7	2	1
TOTAL — 100	19	12	8	6	43	9	2	1
Eclampsia								
Intraven. & Oral	1	2	1				1	1
Oral only	—	—	—				—	—
TOTAL 6	1	2	1				1	1
Hypertension & Preeclampsia.								
Intraven. & Oral	3	1		2		2		
Oral Only	1	1	1	—	1	1		
TOTAL 13	4	2	1	2	1	3		

TABLE II. TIME NECESSARY TO BECOME ALBUMIN AND EDEMA FREE

HOURS	NO. FREE OF ALBUMIN	NO. FREE OF EDEMA
24	14	6
48	4	6
72	2	4
>72	12	15
After delivery	11	9

Delivery.—There were 116 births including 7 sets of twins. Four sets of twins were delivered vaginally and 3 sets by cesarean section. In all, 12 sections were done. Two were for cephalopelvic dysproportion, one for uterine inertia, and the remainder for toxemia. Twenty-nine infants were delivered before 38 weeks, 15 by section and 14 vaginally (Table III). Seven patients are undelivered at the time of this study and 3 we have been unable to trace.

TABLE III. DELIVERY DATA

	TERM	PREMATURE (< 38 WEEKS)	TOTAL
Vaginal	75	14	89
Cesarean section	12	15	27
Total	87	29	116

No maternal deaths occurred in this series but there were 2 neonatal deaths, one from prematurity and one from congenital heart disease. There were four stillbirths. One infant died when a toxic abruptio placentae occurred and the other 3 of causes not discernible. The corrected fetal mortality, omitting the neonatal death due to congenital heart disease, was 4.31 per cent.

The earliest pregnancy terminated was that of an eclamptic patient at 28 to 30 weeks' gestation who was delivered of a 2 pound viable fetus by cesarean section; it died in the neonatal period. This is the case reported in the preliminary study.¹

TABLE IV.
APRESOLINE & PROTOVERATRINE

CASE	Start	Apresoline (amt.)	5min.	10min.	15 min.	20 min.	1 hour	
1.	H.O. B.P.	$\frac{140}{100}$	20mg. I.V.	$\frac{160}{104}$	$\frac{168}{104}$	$\frac{170}{92}$	$\frac{178}{100}$	$\frac{174}{102}$
	PULSE	88		116	120	130	132	142
2.	I. J. B.P.	$\frac{128}{60}$	20 mg. I.V.	$\frac{130}{38}$	$\frac{130}{40}$	$\frac{128}{38}$		$\frac{90}{40}$
	PULSE	80		84	84	84		72
3.	G.B. B.P.	$\frac{164}{100}$	20 mg. I.V.	$\frac{154}{80}$	$\frac{124}{60}$	$\frac{120}{50}$	$\frac{106}{50}$	$\frac{102}{50}$
	PULSE	48		54	60	64	60	60
4.	L. J. B.P.	$\frac{128}{80}$	20 mg. I.V.	$\frac{138}{84}$	$\frac{148}{80}$		$\frac{144}{80}$	$\frac{140}{80}$
	PULSE	80		84	100		100	100
5.	D.H. B.P.	$\frac{128}{72}$	20 mg. I.V.	$\frac{120}{70}$	$\frac{130}{58}$	$\frac{124}{50}$		$\frac{128}{50}$
	PULSE	72		76	96			84
6.	G.M. B.P.	$\frac{138}{96}$	20 mg. I.V.	$\frac{138}{96}$	$\frac{140}{86}$	$\frac{140}{76}$	$\frac{126}{70}$	$\frac{134}{90}$
	PULSE	104		104	128	132	138	120
7.	A.A. B.P.	$\frac{108}{86}$	50 mg. P.O.	$\frac{122}{84}$	$\frac{122}{84}$	$\frac{120}{78}$	$\frac{118}{86}$	$\frac{130}{90}$
	PULSE	92		80	80	80	80	

Apresoline With Protoveratrine

Since we were interested in knowing whether or not Apresoline possibly interrupted any of the reflex actions of protoveratrine, 7 toxemic patients stabilized on protoveratrine were given an acute injection of 20 mg. of 1-hydrazinophthalzine hydrochloride intravenously or 50 mg. orally with the following results (Table IV): systolic blood pressure increased in 3, decreased in 2, and remained essentially unchanged in 2 patients during the first hour. Diastolic pressure dropped in 4 and remained unchanged in 3 instances during this same time interval, while the pulse rate showed the most prominent change with marked increases in 5 cases and a decrease in 2. Acceleration of the pulse rate seemed to be the most constant result with diminution of the diastolic pressure the next most frequent. Although no definite conclusions can be formed from this small group of patients, when tachycardia was produced there might have been interference with the cardiodecelerator reflex action of protoveratrine. Also, increased cardiac output, as evidenced by an elevation of stroke volume (when calculated according to the method of Starr¹²) and an increased pulse rate, may explain those 3 cases in which the systolic pressure increased after Apresoline was given. We now feel that in general Apresoline appears to have a salutary effect when given in addition to protoveratrine, especially in those patients whose blood pressure is difficult to control and in whom an additional decrease in diastolic pressure is desirable.

Comment

It is obvious from the foregoing data that Puroverine is a potent drug and when carefully administered will usually control the cardinal manifestations of the hypertensive toxemias of pregnancy rapidly, effectively, and without the dangers of heavy sedation or interference with adaptive reflexes. Patients are awake and able to take oral nourishment, fluids, and medication, obviating fluid and electrolyte imbalance and simplifying the nursing problem. Although no antepartum sedatives were administered during this study in order to facilitate evaluation of this drug, it appears that basal sedation would be advantageous.

With the release of vasospasm by protoveratrine, the elevated blood pressure was the first symptom to become normal and the other manifestations usually followed, resulting in an apparent regression of a segment of the pathophysiology. In spite of this apparent regression the disease may progress to fetal death without obvious signs. Therefore we feel that evacuation of the uterine contents as early as good clinical judgment permits is indicated in an attempt to deliver a living infant. Increasing levels of blood urea nitrogen and uric acid as well as continuing albuminuria or an unstable blood pressure were important factors in deciding whether or not the need for delivery was imminent. Repeated funduscopic examinations were also invaluable.

At twenty-four hours there was no evidence of oliguria. Toxic manifestations, especially vomiting, could be troublesome but were usually easily controlled. Vomiting and bradycardia responded to atropine and hypotension to the sympathomimetic drugs.

Hydrazinophthalazine hydrochloride as given in this series in cases stabilized with protoveratrine permitted no definite conclusions but the pulse rate usually increased while the diastolic pressure usually fell or remained unchanged. An increase in systolic pressure in some protoveratrine-controlled patients when Apresoline was given may be explained by increased cardiac output. We now feel that this suggests its use in patients in whom blood pressure is difficult to control with protoveratrine alone and especially where diastolic pressure should be additionally reduced.

Summary

1. Protoveratrine (Puroverine) is a potent drug effective orally and intravenously for the release of the vasospasm of toxemia of pregnancy.
2. In spite of apparent control the disease may progress to fetal death, hence delivery is indicated in patients with unstable blood pressure, continuing albuminuria, or increasing levels of blood urea nitrogen and uric acid. Continuing evaluation of the retina by funduscopic examination is also important.
3. No oliguria could be demonstrated twenty-four hours after admission.
4. Toxic manifestations (vomiting, bradycardia, and hypotension) are easily controlled.

5. No fetal deaths were attributable to the drug under study.
6. There is no interference with adaptive reflexes in the doses used.
7. Apresoline may be used to advantage in selected patients in conjunction with protoveratrine.

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THE NEURO-ENDOCRINE PATTERN OF PRE-ECLAMPTIC TOXEMIA

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CONTINUED emphasis has been placed in recent years on the formulation in precise terms of some consistent doctrine which will encompass the major elements of the causative mechanism of toxemia and coalesce disconnected data into a coherent whole, in full agreement with observed facts. In view of the intricacies posed by the problem, its clarification requires a searching analysis of the current ideas of its pathogenesis. In reviewing the various theories which have been advanced in attempts to elucidate the nature of toxemia, one is left with the sobering impression that most of them were purely conjectural and, although they may have contributed some element of constructive thought, they proved insufficient to find acceptance. The present discussion focuses attention on the principal guideposts which seem to provide an adequate basis for defining more accurately the nature of toxemia, combining in one dynamic concept the dominant influence exercised by the over-active hypothalamic-pituitary-adrenal system and the excessive functional sensitivity of the arterioles affecting their pattern of response to hormonal stimuli. Consideration of the state of symbiosis of the maternal and fetal organisms and the ready exchange of abnormal products of metabolism or internal secretion within the blood sinuses surrounding the chorionic villi clarifies various phenomena incident to toxemia.

Current Concepts

Obstetrical opinion had become conditioned to the traditional view that the placenta occupies the pivotal position in the etiology of toxemia by reason of the elaboration of toxic substances. However, attempts to identify chemically or experimentally such toxins in the normal or toxemic placenta were never successful. Moreover, the argument for the placental theory that clinical improvement occurs after the termination of gestation is subject to doubt, the improvement rather being explicable by the cessation of stimuli which are known to activate postpituitary and corticoadrenal secretion. The occurrence in the toxemic placenta of degenerative lesions in gradations from microscopic phenomena to red infarcts has for years received major attention. The storm of controversy that has raged around the question of their etiological significance reflects the uncertainty on the subject. Current opinion tends to regard them as a manifestation rather than a cause of toxemia, particularly in view of recent investigations which define the chromaffin-staining elements in the abdominal sympathetic plexus of the fetus as an accessory tissue to the autonomic nervous system. Structurally identical with the adrenal medulla, the pheochromocytes of the para-aortic organs of Zucker-

kandl represent the main source of pressor amines with a relative noradrenalin content of 98.5 per cent. The fetal circulation is thus considered to be under the regulating influence of the dominating glands of Zuckerkandl which compensate for the absence in the fetus of the adrenal medulla.³ Their product noradrenalin plays the principal part in the mechanism of constriction of the umbilical arteries if the balancing factors—placental acetylcholine and monamineoxidase—are deficient, as in the formation of multiple infarcts. The concomitant enlargement of the reticular zone of the fetal adrenals to about twenty times their relative size in adults poses the problem of another of the intricacies of autonomic factors relating to the fetal economy and circulation. Recent attempts to consider the ischemic placenta in analogy with the ischemic kidney and its renin-pressor mechanism as basic in the toxemic syndrome lack plausibility, since vasopressor principles have never been identified in the normal or toxemic placenta.²³ The interesting demonstration of reduced placental blood flow in the choriodecidual area, as evidenced by a notable delay in the rate at which the directly injected isotonic saline solution was removed from the placental site in pre-eclampsia,¹⁴ might well be referable to degenerative lesions within the placenta or to the reduced blood supply from the uterine wall. Relative anemia of the uterine wall due to constriction of the local arterioles represents the result rather than the cause of toxemia.

The Interrelation of Hormone-Conditioned Systemic Reactions

The view elaborated in this essay brings into focus the multiple causation of the complex symptomatology of toxemia with the spotlight on functional alterations in the endocrine chain. Available evidence indicates that the anterior pituitary-hypothalamic system holds a dominant position in the integration and regulation of the hormonal responses of its target glands. Activated during gestation by constant stimulation from placental derivatives, the pituitary-hypothalamic system plays the vital part in the causation of distinct hormonal alterations in the pregnant organism. Knowledge of the biological characteristics of the endocrine glands during gestation rests upon a solid foundation of established data.² The structural alteration and heightened secretory activities of the pituitary gland, the thyroid, the adrenal cortex, and the paraganglia (Frankenhäuser, Zuckerkandl) are well-supported phenomena.² The posterior pituitary gland, known to be one of the most richly innervated of all glandular structures, is subject to regulation of the production of vasopressin by nerve fibers from the vagus and the supraoptico-hypophyseal tract.²¹ Conglomeration in the anterior pituitary of basophil elements in focal nodular collections in the more severe type of pre-eclampsia is associated with the high gonadotropic content of the serum, and the increased sodium retention with the heightened activity of the outermost layer of the adrenal glands (zona glomerulosa). Collateral evidence derives from the antidiuretic activity after stimulation of the supraoptico-hypophyseal tract, while faradic stimulation of the posterior hypothalamic area produces increased heart rate, increased respiratory rate, vasoconstriction, increased heat

production, increased metabolic activity, corresponding to phenomena in pre-eclamptic toxemia.²¹ Syncytial derivatives and overactivity of the anterior pituitary represent the primary agents responsible for the depletion of glycogen and the elevation of fat in the liver,⁹ a biochemical reaction particularly noticeable in toxemia as described on former occasions.² *In the homeostasis of normal gestation*, the capacity of the Kupffer cells of the normal liver to inactivate the pressor-antidiuretic principle of the postpituitary and adrenal steroids, the function of hepatic and placental monoamineoxidase to neutralize noradrenalin,¹⁰ along with the parasympathomimetic activity of placental acetylcholine, serve as the important *physiological stabilizing and balancing agents* of the physical equilibrium of the arterioles in the maternal and fetal circulation.

The implication of the postpituitary in the basic mechanism of toxemia has been substantially proved. As detailed in preceding articles, the remarkable similarity of the principal manifestations of toxemia and the observations made following the experimental administration of postpituitary extract gave a notable impetus in this direction. The recorded liberation of the pressor hormone from the neurohypophysis by emotional stress or painful stimuli, direct electrical stimulation of the hypothalamic supraoptic nuclei or the central end of the divided vagus nerve supplied corroborative evidence.²¹ The identification in toxemia of the urinary excretion of the antidiuretic principle and of phenylalanine, the representative component of vasopressin, provided relevant information. While the conjugate form of noradrenalin renders its identification in blood exceedingly difficult, abnormal amounts of the catechol amines in the urine in toxemia point to its increased formation or insufficient destruction by monoamineoxidase. Deficient liver function and the presence of noradrenalin play an important part as histamine promoting and liberating principles.¹² Diamine oxidase which destroys histamine is concentrated in the liver and is significantly reduced in toxemia.

Current investigations attribute considerable significance to the hormone sensitization of the arterioles to normal or increased sympathetic pressor impulses. Experiments may be quoted which demonstrate that the pressor effect of noradrenalin may be intensified by the previous administration of adrenocorticotrophic or thyroid hormones,⁶ or histamine. Noradrenalin is now accepted as the principal chemical mediator of sympathetic activity, particularly in regard to the constriction of the arterioles.¹ In pre-eclampsia, a distinct increase in the excretion of corticosteroids occurs as the result of both their elevated level and impairment of liver function. The sensitization or conditioning of blood vessels to pressor agents by certain adrenocortical extracts portrays the active role of the adrenal cortex as a vasopressor component. The evidence of the heightened arteriolar response to postpituitary extract in toxemia is eloquent and convincing, and a similar reaction to noradrenalin exemplifies the altered functional state of the arterioles.

Recent observations concerning a close time relationship between gestation and the manifestation of symptoms of pre-existent yet asymptomatic pheochromocytoma provide relevant data for the consideration of the etiological

significance of *adrenergic factors* in toxemia.¹⁹ Evidence in this direction is offered by the favorable effects of dihydrogenated ergot in pre-eclampsia, particularly the relief of oliguria and anuria,¹⁸ in complete agreement with the experimental observation that ergotoxine and ergotamine block or reverse the activity of adrenergic elements. Correlation of the fact that ganglionic blocking agents such as tetraethyl ammonium exaggerate rather than suppress the hypertensive effects of both epinephrine and noradrenalin with pertinent observations made in toxemia points to the noradrenalin effect. Recent evidence that the benzodioxane compound 933F can be transformed from sympathetic antagonist to sympathetic synergist in the presence of histamine which prevails in toxemia^{5, 16} seriously questions the validity of some contrary opinion based on observations made of late in a few cases of toxemia²² with the administration of the benzodioxane test.

A substantial amount of recent evidence¹³ indicates that vasopressin occurs in the diencephalon and noradrenalin in the posterior hypothalamic area.²¹ Significantly, *deficient tissue oxidation*, primarily representing the result of the overactivity of the posterior pituitary principle² accounts for the increased excitability of the hypothalamic sympathetic centers¹⁵ and for impairment of liver function. Hypoxia greatly increases the output of pressor amines (Bulbring, Burns⁷) and depresses the action of amine oxidase which destroys noradrenalin.^{10, 21} In view of well-documented evidence²⁰ that laboratory animals were rendered hypertensive by being subjected to a choline-free diet, *choline deficiency* in toxemia evolves as a contributing factor in the origin of hypertension.

Summary

The essential cause of pre-eclamptic toxemia appears to be a disturbance of the state of equilibrium of hormonal excitatory and inhibitory factors, associated with heightened reactivity of the arterioles to vasopressor agents and increased excitability of the hypothalamic sympathetic nuclei in response to bombardment by estrogens and impairment of tissue oxidation. In the motivating thought of the alteration of the sympathetic-parasympathetic autonomic balance in such a way as to give a preponderance of influence in toxemia to the former, the rational treatment as governed by understanding of the fundamental cause of the disorder considers the utilization of reserpine as an adrenergic inhibitor and antagonist of Pitressin,¹¹ of Nembutal as a depressor of sympathetic activity, of Veratrum and doryl as parasympathetic stimulants, and of papaverine and magnesium sulfate as long-acting coronary vasodilator drugs, while any drug exhibiting undesirable side effects on the heart is prohibited.

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Addendum.—Concrete advances of recent date relative to the present discussion are worthy of note. A pressor agent closely resembling noradrenalin, designated an intrinsic causal factor of the disorder, has been identified in the blood in toxemia by Gardiner (*J. Obst. & Gynaec. Brit. Emp.*, October, 1955).

Evidence has accumulated of a regulatory mechanism concerning the circulation in the highly contractile portal vessels of the hypophysis and cerebral regions related to the pituitary gland (Spanner: *Klin. Wchnschr.* 30: 47, 1952; Harris: *Bull. Johns Hopkins Hosp.*, November, 1955). Spasm of the arterioles supplying the hypophyseal portal circulation and the initiation of hypoxia cause the manifestation of aberrations of function of the hypothalamic sympathetic centers, attended with the release of noradrenalin and Pitressin (Vogt: *J. Physiol.* 123: 451, 1954).

THROMBOEMBOLIC DISEASE IN OBSTETRICS AND GYNECOLOGY

The Value of Early Diagnosis and Adequate Treatment

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BY THE early diagnosis and adequate treatment of thromboembolic disease several worth-while objectives are achieved: reduction in the incidence of fatal pulmonary emboli; prevention of chronic venous insufficiency and its sequelae (edema, pain, varicosities, skin changes, and ulceration) and, last, reduction in the length of and thereby the cost of hospitalization because of thromboembolic disease. This last point is of importance because of the emphasis that has been placed on the expense of anticoagulant therapy. With these objectives in mind, this survey of the 101 cases of thromboembolic disease occurring in obstetric and gynecologic patients at the Temple University Hospital over a three-year period was undertaken. The incidence of thromboembolic disease on the two services is given in Table I. The difference in incidence between the obstetric and the gynecologic patients can be explained by the fact that vaginal delivery is a physiologic process far less traumatic to pelvic blood vessels than is a pelvic surgical procedure. The incidence of thromboembolic complications following cesarean section and major gynecologic surgery, however, was identical, 1.81 per cent. Of these patients 23 had some form of heart disease, 31 were obese, and 36 had varicosities of the lower extremities. Other contributing factors were anemia in 14, excessive blood loss in 17, and postoperative or postpartum infection.

TABLE I. INCIDENCE OF THROMBOEMBOLIC DISEASE

		NUMBER WITH THROMBOEMBOLIC DISEASE	
<i>Gynecologic Service.—</i>			
Admissions	4,155	50	(1.20%)
Major operations	1,486	27	(1.81%)
<i>Obstetrical Service.—</i>			
Admissions	8,012	51	(0.64%)
Vaginal deliveries	6,552		
Prenatal		10	(0.15%)
Postpartum		36	(0.55%)
Cesarean Section	276	5	(1.81%)

Within certain limitations anticoagulants are now regarded as the specific therapy for thromboembolic disease. It is not unusual, however, for anticoagulant treatment to be delayed until the signs and symptoms are "more definite" in the hope that the condition will subside spontaneously. It is well known that this delay exposes the patient to an increased danger of pul-

monary emboli; however, the effects of this delay on the duration of the disease and the hospital stay tend to be overlooked. In order to determine the effects of this delay on the duration of the disease and the length of hospitalization, the patients were divided into 3 groups on a basis of the time at which anticoagulant therapy was begun (Table II). Those cases in which there was no delay in diagnosis and in which anticoagulant therapy was begun immediately were placed in Group I. Those in which there was a delay of from one to two days in initiating treatment were placed in Group II, and Group III included all cases in which treatment was begun more than two days after the initial symptoms. The duration of the disease was determined from the time of the first sign or symptom to the absence of any objective signs of disease activity. The increase in hospital stay was determined by subtracting the expected discharge date for that particular patient from the date of discharge after treatment for thromboembolic disease was completed. Because of insufficient data, only 67 of the 101 cases are included. The cases are almost evenly divided between the two services.

TABLE II. EFFECT OF TIME OF BEGINNING OF ANTICOAGULANT TREATMENT

TIME OF BEGINNING OF TREATMENT	I. IMMEDIATE (29 CASES)	II. WITHIN 48 HOURS (20 CASES)	III. AFTER 48 HOURS (18 CASES)
Duration of disease (days)	3.1	5.4	11.2
Bed rest	4.2	6.0	8.8
Increased hospital stay	2.6	7.0	10.4

Duration of Disease and Hospital Stay

The duration of disease in the 29 patients in Group I was 3.1 days. They were on bed rest an average of 4.2 days and their hospital stay was increased by only 2.6 days. With treatment one to two days later (Group II) the hospital stay was increased by 7.0 days. There was also an increase in duration of disease to 5.4 days and in bed rest to 6.0 days. The excessive delay in beginning anticoagulant therapy for the 18 cases in Group III resulted in an increase in hospital stay of 10.4 days. The duration of the disease was 11.2 days and 8.8 days of bed rest were necessary.

Delay in the institution of anticoagulant therapy is associated with an increase in the duration of the disease and in the length of the hospital stay. Awareness of this should further encourage early diagnosis.

Sequelae

Regardless of the time of beginning of therapy only 4 of the 67 patients treated with anticoagulants have developed chronic venous insufficiency (Table III). Of the patients who did not receive heparin or Dicumarol, only 21 are available for follow-up study. It is significant, however, that already 9 of these 21 inadequately treated patients have moderate to marked chronic venous insufficiency. Since all of these cases are of relatively recent origin they do not represent the total expected late venous sequelae, yet the contrast between the results of adequate and inadequate therapy is rather evident.

According to Bauer¹ the prevention of chronic venous insufficiency depends upon detection and adequate treatment of the disease while in its earliest stage in order to confine it to the calf and prevent extension to the thigh. Zilliacus² made a follow-up study of 609 cases of thrombophlebitis treated with

heparin or Dicumarol and found that the mean index of sequelae with the disease confined to the calf was approximately one-half that which occurred when the disease had extended to the thigh. Further, Bauer states that in 90 per cent of a series of 357 cases from a general hospital the diagnosis was made while the disease was confined to the calf. In contrast, approximately one-half of our cases drawn solely from the obstetric and gynecologic services had involvement of the femoral or pelvic veins at the onset (Table IV).

TABLE III. SEQUELAE. CHRONIC VENOUS INSUFFICIENCY

TYPE OF TREATMENT	ADEQUATE (ANTICOAGULANTS)	INADEQUATE
Number of cases	67	21
Sequelae	4	9

TABLE IV. SITE OF ONSET OF THROMBOEMBOLIC DISEASE

SITE OF ONSET	OBSTETRIC	GYNECOLOGIC	TOTAL
Calf	23	25	48
Calf and femoral	19	14	33
Femoral	1	1	2
Pelvis	7	6	13
Embolus	1	4	5

Pulmonary Embolism

Pulmonary embolism occurred in 7 of the 101 patients, once in an obstetric patient and 6 times in gynecologic patients. The pulmonary embolus was the initial symptom in 5 of the 7 cases and in one of these it was sudden and fatal.

CASE 1.—(Hospital No. 159575.) This 42-year-old Negro, para 0, gravida 0, was admitted to the gynecologic ward on July 28, 1950, and died on July 29, 1950. Her only complaints on admission were progressive dyspnea on exertion and an abdominal mass. Examination revealed an enlarged heart and liver and a fibroid uterus. The blood pressure was 134/96, hemoglobin 8.3 Gm., and blood sugar 165 mg. per cent. The patient was afebrile. On July 29, she received 500 c.c. of compatible blood. After 200 c.c. of blood had been absorbed the patient sat up in bed complaining of severe dyspnea and was noted to be cold and clammy with a blood pressure of 80/60, pulse 140 per minute, and respirations 40 per minute. She experienced no pain and died twelve minutes after the onset of symptoms.

At postmortem examination a large antemortem clot in the left pulmonary artery just proximal to its main branches was found. No thrombi were found in the pelvic veins; the leg veins were not dissected.

The remaining 4 cases in which the pulmonary embolus was the initial symptom occurred following pelvic surgical procedures (2), delivery (1), and in association with pelvic malignancy (1). The emboli occurred on the second and third days following operation and on the fifth day post partum.

Of the 2 instances in which the embolus was preceded by thrombophlebitis, one occurred on the tenth day postoperatively during Dicumarol treatment for thrombophlebitis. The prothrombin time had risen from 28 per cent of normal on the ninth postoperative day to 38 per cent of normal on the day of the embolus. Anticoagulant therapy was increased and pain was effectively relieved by a stellate block. The remaining patient had a recurrent episode of thrombophlebitis and multiple pulmonary emboli associated with terminal carcinoma of the cervix with ureteral obstruction and was untreated.

Diagnosis

Because the early diagnosis and initiation of active adequate therapy are important, some of the aspects of diagnosis and therapy in obstetric and gynecologic patients must be discussed since they may differ somewhat from those in the medical or general surgical patient. No attempt will be made to outline all the diagnostic points which are well summarized in the literature, but several should be stressed. In these patients tenderness over the involved veins was the one most reliable diagnostic sign. The most frequent site of tenderness was the middle third of the calf, although the femoral and pelvic veins were frequently involved. The femoral vein can be isolated just medial to the pulsation of the femoral artery in Scarpa's triangle and the tenderness here is practically pathognomonic of femoral thrombophlebitis. Occasionally the physician is lulled by the absence of fever, yet 23 patients had no temperature elevation either at the onset or during active recurrences of the disease. Six of the 10 prenatal patients were in this group. The time of onset was variable, averaging 5.5 days following operation or delivery; 40 cases began within the first four postoperative or postpartum days.

POSTPARTUM PELVIC THROMBOPHLEBITIS (Response to Dicumarol)

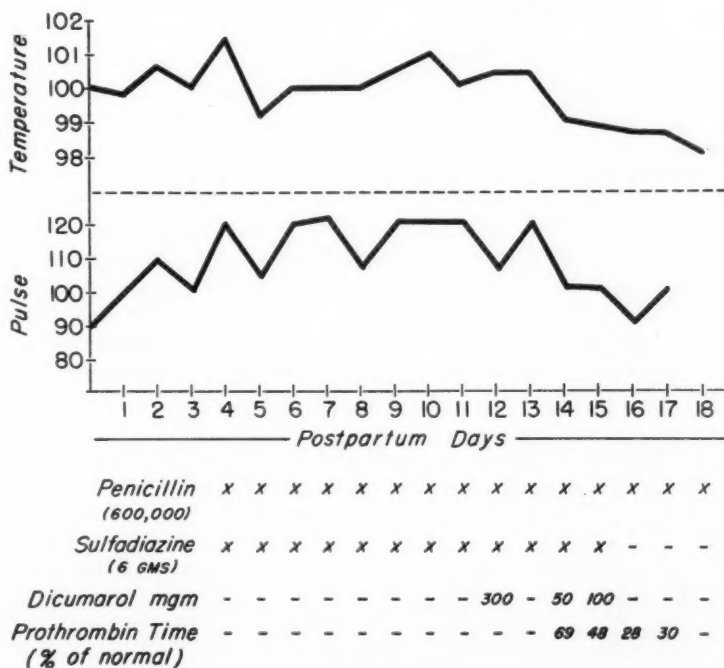


Fig. 1.

The diagnosis of *pelvic thrombophlebitis* was especially difficult and was often delayed. The lesion was usually recognized after failure of response to therapy for endometritis, parametritis, cellulitis, or pelvic peritonitis. Nine of the 13 patients with pelvic thrombophlebitis had one of the above infections but despite antibiotic therapy the fever subsided only after an adequate level of anticoagulants was obtained. This has been noted by Wolf.³ The following two case reports illustrate this.

CASE 2.—(Hospital No. 133120.) A 26-year-old Negro woman, para 0, gravida i, was delivered with outlet forceps at term. Labor was complicated only by a mild premature separation of the placenta. The patient was febrile following delivery and on the fourth postpartum day a diagnosis of endometritis and parametritis was made by pelvic examination and treatment with penicillin and sulfadiazine was begun. Because of the continued febrile reaction and abdominal pains pelvic examination was repeated on the twelfth postpartum day and a diagnosis of left broad ligament thrombophlebitis and pelvic cellulitis was made. Treatment with Dicumarol was advised and was begun that day. The return of the temperature to normal coincided with the therapeutic depression of the prothrombin time (Fig. 1).

POSTPARTUM PELVIC THROMBOPHLEBITIS
(Response to Heparin & Dicumarol)

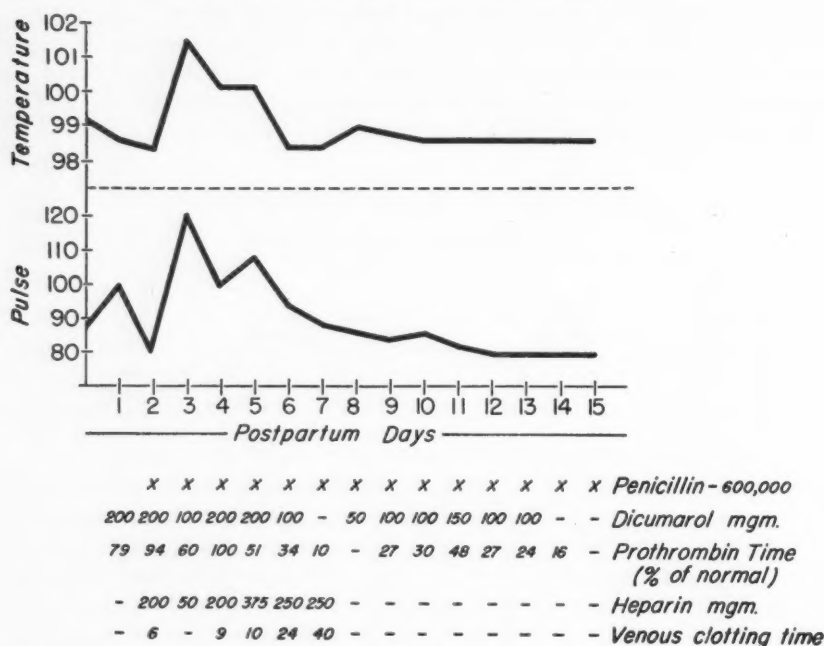


Fig. 2.

CASE 3.—(Hospital No. 135492.) A 33-year-old white para vi, gravida x, had a spontaneous delivery on Aug. 23, 1950. During her prenatal course she had two episodes of thrombophlebitis which were treated with heparin and the Trendelenburg position in the hospital. The legs showed no evidence of active involvement at the time of delivery but thrombophlebitis became evident on the first postpartum day and gradually involved the calf, femoral and pelvic veins. Two hundred milligrams of Dicumarol had been given prophylactically after delivery and the next day active treatment was begun with 200 mg. Dicumarol and 200 mg. Depoheparin subcutaneously and was continued with both these preparations. On the sixth postpartum day the abdominal symptoms were of such severity that surgical consultation was requested to aid in ruling out an acute process requiring operation. Continued administration of anticoagulants was advised and the symptoms subsided the next day, 24 hours after a therapeutic level had been obtained (Fig. 2).

The diagnostic features of pelvic thrombophlebitis are vague and there may well have been more cases than are included here. A number of patients with vague postoperative or postpartum pelvic pain who are labeled as having pelvic inflammatory disease may well have chronic pelvic thrombophlebitis. It is unfortunate that the diagnosis usually is made because of failure of re-

sponse to other measures to combat pelvic infection; however, with careful palpation one may discover the tender veins on the lateral pelvic wall or in the broad ligament.

Treatment

The fundamental principles of therapy consist of treatment directed toward prevention of the propagation and dislodgment of the clot. These are accomplished by attacking the clotting process with the immediate administration of heparin and Dicumarol and by increasing the circulation of the blood in the extremities with the Trendelenburg position.^{4, 5} The dosage of the anticoagulants varies from patient to patient but the most important factor is that it be adequate to maintain the venous clotting time (Lee-White) from 15 to 30 minutes and the prothrombin time between 15 and 30 per cent of normal. The Trendelenburg position to increase the circulation of blood in the lower extremities has been somewhat neglected but should be included. The extremities must be elevated above the level of the heart and the only way this can be accomplished without compressing the femoral veins is by elevating the foot of the bed, the patient remaining in the recumbent position.

In addition to the anticoagulant therapy antibiotics should be administered. It has been demonstrated in animal experiments that heparin and penicillin together have a greater effect on the suppurative thrombus than either drug used alone.⁶ While there has been concern over penicillin and Aureomycin increasing the coagulability of the blood the evidence is now against this.^{7, 8}

When pain is severe paravertebral block usually gives dramatic relief⁹; procaine¹⁰ (0.5 Gm. in 500 c.c. fluid) intravenously given over a 20 minute period is less effective and of shorter duration. Spinal anesthesia is inferior to either; although it relieves the pain temporarily it causes muscular paralysis and pooling of blood in the lower extremities, thereby increasing stasis. Neither paravertebral block nor spinal anesthesia should be used, however, after anticoagulant therapy has been initiated.^{11, 12}

When the symptoms begin to subside, the patient should begin active leg exercises but should remain in bed until the signs and symptoms are absent, the temperature is normal for a 24 hour period, and the anticoagulant level is adequate. If edema is present on arising an Ace bandage is applied. Heparin, when used alone, must be continued in therapeutic amounts at least 24 hours after ambulation and in decreasing amounts for 2 or 3 more days. Dicumarol should be continued in therapeutic dosage approximately 5 to 7 days after ambulation and in slowly decreasing amounts thereafter for a total of 3 to 4 weeks of treatment.¹³ Once the patient's response to Dicumarol is evaluated in the hospital it can be continued with relative safety after discharge with regular prothrombin checks.

That anticoagulant therapy for thromboembolic disease is as essential during pregnancy as at any other time is attested by the 15 per cent mortality in the 80 cases of antepartum thromboembolic diseases untreated by anticoagulants collected from the literature by Mansell.¹⁴ In antepartum thromboembolic disease heparin is the drug of choice and was used without complication in the prenatal patients in this series. (In one case the venous clotting time was inadvertently increased to over one hour without maternal or fetal hemorrhage.) Heparin has been used experimentally in the treatment of toxemia of pregnancy without adverse effect^{15, 16} and Jorpes¹⁷ has recommended it in the therapy of prenatal thrombophlebitis. The administration of Dicumarol has resulted in retroplacental bleeding and stillbirth^{18, 19} in animal experiments and intrauterine fetal death has been reported following its use in the prenatal period.²⁰ However, the literature now contains a number

of reports of successful antepartum coumarin therapy.^{14, 21} It is this author's opinion, though, that its cautious use should be restricted to only those cases in which prolonged therapy will be necessary.

There has been hesitancy in initiating therapy with the anticoagulants post partum because of the fear of hemorrhage but Barnes²² has demonstrated no increased blood loss in normal postpartum patients after heparin or Dicumarol. In our cases heparin and Dicumarol were begun immediately following operation or delivery when indicated. During the first 24 hours the clotting times were very carefully checked. When prophylactic anticoagulants were considered, very careful attention was applied to hemostasis at operation or delivery. With extensive pelvic procedures with large open surfaces that could readily bleed, anticoagulants were deferred for 24 to 48 hours and the Trendelenburg position alone was utilized. Prophylactic Dicumarol has been recommended at the onset of labor but, in view of the unpredictable nature of labor and delivery, it seems that in the inevitable cases of prolonged labor with difficult forceps delivery or cesarean section an unnecessary complication has been added. One would at times have to rely on a rapid reversal of the hypoprothrombinemia with vitamin K at a time when the maternal reserves are greatly diminished. The course of labor in patients with active thrombophlebitis should be closely followed. Heparin should be given until the onset of labor and in the absence of unusual postpartum bleeding should be resumed approximately four hours after delivery. Protamine sulfate and fresh blood should be on hand. There is no reason for cesarean section in these patients except for specific obstetric indications. Dicumarol post partum has little apparent effect on the nursing infant²³ although when it is used early or over a long period of time the infant should probably be protected with vitamin K.

Pulmonary embolism demands energetic treatment with heparin²⁴ and Dicumarol. Oxygen and papaverine are well known and valuable emergency measures. While our experience with stellate block has been limited to one case, the result was excellent. It should prove a worth-while procedure in cases of pulmonary embolism with severe pain and dyspnea.

Complications

Of the 81 patients who received anticoagulants 4 had major hemorrhages resulting from the treatment. Two occurred on the first and second days, respectively, after biopsy of the cervix and were controlled by suture, water-soluble vitamin K (48 and 60 mg. intravenously) and transfusions of fresh blood. One followed heparin and Dicumarol therapy begun 3 days after a panhysterectomy. The hemorrhagic tendency was manifested by cuff bleeding on the seventh day which was controlled by suture and fresh-blood transfusion. The Dicumarol was continued and on the twelfth postoperative day a wound hematoma was discovered. Dicumarol was discontinued and the patient had an uneventful recovery after secondary closure of the abdominal wound. The last patient, a 270 pound elderly white woman, had an unrecognized thrombophlebitis prior to radical hysterectomy for carcinoma of the corpus. The prothrombin time during a previous hospital admission had been 20 per cent of normal without treatment. The thrombophlebitis recurred the second day after operation and treatment with heparin and Dicumarol was begun. The temperature was typical of sepsis and on the fifth day a wound hematoma with a coexisting wound infection was noted. This was controlled with 120 mg. of vitamin K intravenously and 1,000 c.c. of fresh blood. Anticoagulants were discontinued and subsequent secondary closure was followed by a prolonged but otherwise uneventful convalescence. In retrospect, the

low prothrombin time on the first admission was probably a manifestation of chronic liver disease and the patient should not have received Dicumarol.

Mortality

There were two deaths, the first of which was summarized previously and the second is discussed below:

CASE 4.—(Hospital No. 146419.) A 32-year-old white para iv, gravida v, was delivered spontaneously on May 11, 1949, and was discharged on the ninth postpartum day asymptomatic and afebrile. On the seventeenth postpartum day she developed soreness in the left leg and was treated by her family physician with penicillin. Within 24 hours the leg was swollen, mottled, and tender but ambulatory treatment with penicillin was continued at home. Finally, on the twenty-first postpartum day at which time thrombophlebitis also involved the right leg, she was referred to the hospital for treatment.

Examination disclosed an indurated tender left femoral vein with 2 plus edema on the left and 1 plus on the right leg. Moses' and Homans' signs were positive bilaterally. The blood pressure was 108/74, pulse 80, and temperature 99° F.

Treatment was begun with 300 mg. Dicumarol and spinal anesthesia with 5 mg. Pontocaine, 4 mg. Neosynephrine, and 1 c.c. of 10 per cent dextrose preceded by the intramuscular injection of 24 mg. of ephedrine sulfate. The spinal anesthetic, given at the third lumbar vertebra with a No. 20 gauge needle after a clear tap, completely relieved the pain. The anesthetic level reached the tenth thoracic vertebra. The blood pressure was 120/70 before and 106/80 twenty minutes after the spinal anesthetic. One-half hour afterward the patient complained of a headache and the blood pressure was 150/98. Forty-five minutes later the blood pressure was 170/110, the patient vomited, was difficult to arouse, and had hyperactive reflexes of the right arm and loss of all tone. The left pupil was dilated and fixed and the right contracted. Spinal tap revealed a pressure of 300 mm. H₂O and 28 c.c. of grossly bloody fluid was removed. Synkayvite, 60 mg., and 500 c.c. of blood were given. A left subtemporal decompression was done and extensive subarachnoid and minimal intracerebral hemorrhage was found, but no single specific bleeding site was detected. The postoperative condition was poor and the patient died 34 hours later.

While the final diagnosis was subarachnoid hemorrhage, there are several contributory factors which must be evaluated. Duff²⁵ has reported several instances of subarachnoid and cerebral hemorrhage in elderly hypertensive patients treated with large amounts of Dicumarol; however, the onset within 2 hours of the initial 300 mg. dose of Dicumarol seems to rule out this possibility. The second consideration is the effect of the vasopressors, ephedrine intramuscularly and Neosynephrine intrathecally. The evidence here is not clear-cut since the blood pressure remained normal twenty minutes after the beginning of anesthesia. In retrospect, however, the use of the vasopressors was unwise.

Summary

In addition to reducing the incidence of fatal pulmonary emboli and chronic venous insufficiency the early and adequate treatment of thromboembolic disease greatly diminishes the hospital stay of these patients. It also shortens the duration of the disease and the period of bed rest. The average increase in hospital stay of 2.6 days in those patients treated early and adequately is 7.8 days less than the hospital stay of the patients treated adequately but late. The cost of this additional hospitalization is much more than that of the usual course of anticoagulant therapy; hence the expense of the anticoagulants should not be a consideration in initiating treatment. Also,

with inadequate treatment, the patient's chances are greatly increased of poor functioning of the leg, which results in a lifelong disability with its consequent expense and diminished earning power.

The major etiological factors were summarized and, as emphasized in other reports, it is important to recognize the role played by heart disease, obesity, anemia, varicosities, hemorrhage, and morbidity. Aside from cesarean section, the type of delivery had little influence on the incidence of thromboembolic disease.

A few of the diagnostic features are discussed in detail. Contrary to other reports, an unusual number of these patients had femoral or pelvic thrombophlebitis at the onset. An explanation for this is that the trauma of both operation and delivery in gynecology and obstetrics is centered on the pelvic veins and an increased incidence of thrombophlebitis in these vessels should be expected. An elevation in temperature was not always present at the onset or during the course of the disease despite other signs of active thrombophlebitis.

Pelvic thrombophlebitis is usually associated with pelvic infection and is rather difficult to diagnose. The lack of response to the antibiotics alone and the marked improvement which occurs when the anticoagulants are added is often the most conclusive diagnostic finding, although by careful pelvic examination the involved veins may sometimes be palpated. The response to treatment in the cases of pelvic thrombophlebitis was satisfactory and vena cava ligation was not necessary. However, the two cases of chronic venous insufficiency treated by deep femoral vein ligation were improved.

The fundamentals of treatment with the anticoagulants, antibiotics, and the Trendelenburg position are well known. The accessory procedures such as paravertebral block and intravenous procaine have a definite place in therapy in selected cases. The time of ambulation has been difficult to decide but if it is begun when the anticoagulant level is within therapeutic range, the signs and symptoms are absent, and the temperature has been normal for a 24 hour period, a minimum of complications will arise. Prenatal patients should receive heparin alone unless prolonged therapy is necessary, in which event Dicumarol may be used with caution. Both heparin and Dicumarol may be begun immediately following delivery and operation when indicated.

The complications due to anticoagulants were few in number and may be kept at a minimum by careful clinical supervision. In general heparin causes fewer hemorrhagic complications than Dicumarol and these can be rapidly reversed with protamine sulfate and blood transfusion. The potential dangers of anticoagulant therapy must be remembered and the anticoagulants should be used only under careful clinical observation and laboratory control.

Conclusion

The early and adequate treatment of thromboembolic disease has the following advantages:

1. Reduction in the incidence of fatal pulmonary emboli.

2. Prevention of chronic venous insufficiency.
3. Reduction of the hospital stay, the period of bed rest, and the duration of the disease.

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902 NORTH 3RD STREET

PREGNANCY AFTER FORTY-FOUR*

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DISCUSSION of the outcome of pregnancy in the very late years of the childbearing period reveals the fact that there are few figures to substantiate the impressions one may have on the subject. Much has been written on the elderly primipara^{1, 2} and some on the "dangerous multipara." An examination of the literature, however, does not give any answers to a considerable number of questions, such as the incidence of pregnancy in the late years, the probable outcome of pregnancy in the woman in the last few years of her reproductive life, the ratio of term gestation to abortion, the relative degree of the hazards to which the mother is subjected in comparison to pregnancy in the earlier years, the likelihood of abnormalities of birth, and many others. A report by Davis and Seski³ of the University of Chicago in which they studied a series of 1,011 consecutive cases of pregnancy in women over 40 years of age may be compared with the present report.

A number of impressions exist which can be somewhat clarified. The U. S. Vital Statistics,⁴ for example, indicate that pregnancy after 50 years of age is fairly common. However, individual hospital series including our own show it to be very rare. We had the impression that the relative incidence of abortion was very much higher in the late forties than in the earlier years. There are not many figures available to indicate this, but the present series confirms this impression. We know that congenital abnormalities are progressively more frequent as the age of the mother advances. Is the woman in the late forties more likely to produce an abnormal child than when she was when she was 5 to 10 years younger? Apparently so.

In this paper we have considered cases involving pregnancy in women 44 years of age and over who were admitted to the New York Lying-In Hospital during the twenty-year period from 1932 to 1953.

Table I shows that there were 160 viable births in 65,880 deliveries and 77 early pregnancies in 5,947 abortions. This gives a total of 237 patients 44 years of age and over in 71,827 pregnancies, an incidence of 1 in 303.

We see from Table II that the incidence of abortion in this series is 33 per cent. In contrast to this, the over-all incidence of abortion at New York Lying-In Hospital⁵ for a twenty-year period was 8.3 per cent. That at the Chicago Lying-in Hospital in the series presented by Davis and Seski of 1,011 pregnancies in women over 40 years of age was 4.9 per cent.

Table III shows the age distribution for the viable births and the abortions. It will be seen that there were few pregnancies after 47, but proportionally four times as many abortions as viable births. There was no viable pregnancy after 50 and only 3 abortions.

*Presented at a meeting of the New York Obstetrical Society, Dec. 14, 1954.

TABLE I. PREGNANCIES IN WOMEN OVER 44 YEARS OF AGE, NEW YORK LYING-IN HOSPITAL

Viable births	160	Total deliveries (1932-1953)	65,880
Abortions	77	Total abortions (1932-1953)	5,947
Pregnancies in women over 44	237	Total admissions involving pregnancy (1932-1953)	71,827
Incidence 1:303			

TABLE II. ABORTIONS IN WOMEN OVER 44 YEARS OF AGE

Viable births	160	
Abortions	77	
Incidence of abortion		33.0%
New York Lying-In: Abortions in total pregnancies (1932-1953)		8.3%
Chicago Lying-In: Abortions in 1,011 Women Over 40 (52,128 pregnancies)		4.9%

TABLE III. AGE DISTRIBUTION AND OUTCOME IN PREGNANCIES AFTER AGE 44,
NEW YORK LYING-IN HOSPITAL
(237 CASES)

OUTCOME	AGE									
	44	45	46	47	48	49	50	51	52	53
Viable births (160 cases)	75	52	25	5	2	1	0	0	0	0
Abortions (77 cases)	30	16	15	7	4	2	0	1	0	2

Incidence of Viable Births After 46 in Relation to Age.—

Term pregnancy in women 46 years of age and over is not common and Table IV presents a large series of cases from several maternity hospitals. We have more cases in the 46 and 47 year age group than the other hospitals for some unexplained reason. In this total of nearly 300,000 deliveries there was no one 50 years of age or over and only three 49 years of age; however, we cannot be entirely certain of the correct ages of these three. We have added to this list the New York City Vital Statistics⁶ for a ten-year period from 1940 to 1950 which show 20 deliveries by women 50 years of age or over in 1.5 million deliveries. In addition they show that, in 120,784 fetal deaths in this same period, 30 of the mothers were 50 years of age or over. The ratio of whites and nonwhites was the same. In this connection it has to be remembered that a very great percentage of the women included in the New York City figures are of foreign birth and uncertain of their exact age.

TABLE IV. INCIDENCE OF VIABLE BIRTHS AFTER 46 IN RELATION TO AGE

HOSPITAL	TOTAL NO. OF CASES	AGE						
		46	47	48	49	50	50 PLUS	
Chicago Lying-in Hospital ³	50,000	2	0	2	0	0	0	
Johns Hopkins Hospital ¹¹	65,000	3	2	0	1	0	0	
Boston Lying-in Hospital ¹²	50,000	-	-	-	1	0	0	
Jersey City Medical Center ¹³	42,000	10	4	3	0	0	0	
Lenox Hill Hospital ¹⁴	27,273	6	5	1	0	0	0	
New York Lying-In Hospital	65,880	25	5	2	1	0	0	
New York City Statistics ⁶	1,427,106	-	-	-	-	-	20	

In further contrast to the various hospital statistics quoted above, we find that U. S. Vital Statistics⁴ for 1948 gave an incidence of 1 birth in 20,000

in women 50 years of age or older. The ratio of Negro to white women in these statistics is 3:1 but the accuracy of these ages is questionable. Gilbertson,⁷ DeLee and Greenhill,⁸ and Berkeley, Bonney, and MacLeod⁹ have had women 50, 52, and 51 years of age who delivered. Apparently parturition in women over 52 years of age has not been proved.

Eastman¹⁰ writes that pregnancy in women 48 years of age and over is very rare. This statement is in part confirmed by Table III, particularly in regard to viable births, as there were only 3 cases in our 66,000 deliveries. There were a number of cases however, which ended in abortion, either suspected or unsuspected, which fall into this group. Table III showed that there were 4 who were 48, 2 who were 49, 1 who was 51, and 2 who were 53 years of age.

Parity.—

Table V shows that 27, or 17 per cent of the 160 viable births, occurred in primiparas. There was, however, no primipara who had reached the age of 46 who delivered a living child. Labors in the primiparas were of the usual duration except for 2 prolonged ones. Eight of the 27 deliveries were by cesarean section and 10 were operative. The incidence of toxemia was also high. All but 5 of these 27 women were pregnant for the first time. Two stillbirths occurred, both macerated, and one was in the 46-year-old patient.

TABLE V. TERM DELIVERIES IN PRIMIPARAS. 27 CASES, INCIDENCE 17 PER CENT

		NO. OF CASES
<i>Ages.</i> —		
	44 years	14
	45 years	12
	46 years	1
<i>Type of Labor.</i> —		
	Average	25
	Prolonged	2
<i>Antenatal Complications.</i> —		
	Toxemias	4
	Others	2
	None	21
<i>Type of Delivery.</i> —		
	Spontaneous	9
	Forceps	10
	Cesarean	8
<i>Outcome.</i> —		
	Alive	25
	Perinatal deaths	2

TABLE VI. ABORTIONS IN PRIMIPARAS. 9 CASES, INCIDENCE 11.7 PER CENT

		NO. OF CASES
<i>Ages.</i> —		
	44	3
	45	2
	46	3
	47	1
<i>Antenatal complications.</i> —		
	Hypertensive cardiovascular disease	2
	None	7
<i>Preoperative diagnosis.</i> —		
	Incomplete abortion	5
	Menometrorrhagia	4
<i>Pathology.</i> —		
	Decidua	4
	Fetal membrane	3
	Hyaline degeneration	2

Table VI shows that 9, or 11.7 per cent of the 77 abortions, were in primiparas. Five of these were pregnant for the first time and 2 had had previous pregnancies also ending in miscarriages. Antenatal complications were not important. Five cases were diagnosed preoperatively as abortions and all were confirmed pathologically. Only 3 showed fetal membranes, however.

Method of Delivery.—

Pregnancy terminated spontaneously in 103, or 64 per cent of the cases, as seen in Table VII, which compares with an over-all hospital incidence of 76 per cent in 1933 and 63 per cent in 1953. There were 17 cesarean sections, a rate of 10.7, compared with the hospital rate of 2 per cent in 1933 and 4.4 per cent in 1953. Forceps and breech deliveries were performed with essentially the same frequency as the service rate. Version and breech extraction were resorted to on 3 occasions which made a relatively high incidence. One of these 3 babies died from a complication of a birth injury.

TABLE VII. METHOD OF DELIVERY

METHOD	NO. OF CASES	INCIDENCE (%)	INCIDENCE NEW YORK LYING-IN	
			1933 (%)	1953 (%)
Spontaneous delivery	103	64.0	76.0	63.0
Cesarean section	17	10.7	2.0	4.4
Midforceps	13	8.1	4.1	12.9
Low forceps	11	6.9	8.5	15.8
Version and extraction	3	1.9	0.45	0.2
Breech extraction	4	2.5		
Assisted breech	9	5.6	3.7	3.0
Total	160			

The 17 cesarean sections shown in Table VIII were performed for the usual indications. Five were for disproportion and 3 were for bleeding. There was one fetal death of a macerated infant in which case a cesarean hysterectomy was done.

TABLE VIII. CESAREAN SECTIONS. 17 CASES, INCIDENCE 10.7 PER CENT

INDICATIONS	NO. OF CASES
Previous cesarean section	3
Placenta previa	2
Preventive separation	1
Disproportion	5
Breech	2
Jaundice	1
Toxemia	1
Transverse myelopathy	1
Infection	1
<i>Comparative Incidence</i>	
<i>New York Lying-In.—</i>	
Above series	10.7%
1953 average	4.4%
<i>Chicago Lying-in.—</i>	
Cases after 40	13.3%
Seventeen-year average	4.4%

There were 16 cases, as seen in Table IX, in which labor was prolonged over thirty hours. Nine of these patients delivered spontaneously and none required cesarean section. Five of these babies, however, did not survive.

One was an 1,800 gram premature infant born by assisted breech who died on the fifth day, the second born by breech extraction did not respond to resuscitation, the third was a deadborn infant with congenitally abnormal kidneys, and the fourth a deadborn macerated infant. The fifth had a questionable cerebral birth injury and died on the sixty-third day of meningitis. The incidence of 10 per cent can be compared to the 1953 New York Lying-In Hospital incidence of 1.1 per cent.

TABLE IX. PROLONGED LABOR, OVER THIRTY HOURS. 16 CASES, INCIDENCE 10 PER CENT

	NO. OF CASES
<i>Ages.</i> —	
44	8
45	5
46	3
<i>Parity.</i> —	
Primiparas	2
Multiparas	15
<i>Method of Delivery.</i> —	
Spontaneous	9
Forceps	3
Breech extraction	4
<i>Outcome.</i> —	
Normal	11
Perinatal deaths	5
<i>Comparative Incidence</i>	
Present series	10%
New York Lying-In, 1953	1.1%

In Table X it is interesting to note that nearly one-third of the 77 abortion cases came to surgery without a diagnosis of pregnancy. These were classified as menometrorrhagia. Nine patients received a therapeutic abortion. Two abortions were discovered following operation other than a dilatation and curettage.

TABLE X. INDICATIONS FOR DILATATION AND CURETTAGE IN ABORTIONS

INDICATIONS	NO. OF CASES
Incidental to other surgery	2
Therapeutic abortion	9
Spontaneous abortion	7
Menometrorrhagia	24
Incidental to other surgery	2
Total	77

Antenatal Complications.—

Antenatal complications occurred in 46 women of the 160 who had viable births. As seen from Table XI the majority of the complications concerned the cardiovascular system. Twenty-two patients developed toxemia; 4 of these were primiparas. Hypertensive disease without toxemia was present in 9 patients, none of whom were primiparas. This total of 31 cases gives an incidence of 19.4 per cent compared to that of 5.3 per cent for 1953 at New York Lying-In Hospital. The 5.3 per cent figure, however, includes abortions. When abortions are included in the figure, the 19.4 per cent is reduced to 15.6 per cent. This incidence of three times our over-all hospital incidence agrees with the figure given in the Chicago Lying-in report previously quoted.

There were 10 cases of severe pre-eclampsia, an incidence of 6.3 per cent as compared to that of 0.7 per cent for 1953 on our service at New York Lying-In.

Heart disease occurred in 7.5 per cent of the cases, nearly twice the annual incidence. This is reduced somewhat to 6.7 per cent when abortions are included for a comparative figure.

Two cases of placenta previa and one of premature separation of the placenta were encountered, which was about the average incidence. Myomas were surprisingly infrequent.

TABLE XI. ANTENATAL COMPLICATIONS IN VIABLE BIRTHS. 46 CASES, INCIDENCE 29 PER CENT

	NO. OF CASES	INCIDENCE (%)	
		PRESENT SERIES	NEW YORK LYING-IN, 1953 (INCLUDES ABORTIONS)
<i>Ages.</i> —	28		
44	12		
45	6		
46			
<i>Toxemia.</i> —			
Mild	12		
Severe	10	6.3	0.7
<i>Hypertension.</i> —			
Mild	6		
Severe	3	31	5.3
Pyelonephritis	2		
<i>Heart disease.</i> —			
Rheumatic	4		
Hypertensive cardiovascular	8	12	7.5
4.3			
<i>Hemorrhage.</i> —			
Placenta previa	2		
Premature separation	1	3	1.8
1.2			
Myoma	1		
Others	6		

The complications involving the abortions were more varied. One-third or 25 of the cases had complications, as shown in Table XII. Hydatid mole occurred in 6 cases, an incidence of 2.5 per cent in all pregnancies in this series. The over-all incidence on our hospital service for 1952 and 1953 was 0.11 per cent of all pregnancies. All 4 instances of the hypertensive cardiovascular disease were mild as were the 2 cases of hypertension. There were 4 patients who had myomas. Therapeutic interruption of pregnancy was performed in the 3 cases of psychosis. A scattering of entities made up the remainder of the complications, including hyperthyroidism, multiple sclerosis, and tuberculosis.

TABLE XII. ANTENATAL COMPLICATIONS IN ABORTIONS. 25 CASES, INCIDENCE 32.5 PER CENT

	NO. OF CASES
<i>Ages.</i> —	
44	9
45	3
46	4
47	6
Over 48	3
Hypertensive cardiovascular disease, mild	4
Hypertension	2
Myoma	4
Psychosis	3
Mole	6*
Others	6
<i>Incidence of Mole.</i> —	
Present series	2.5%
New York Lying-In, 1953	0.11%

Maternal Mortality.—

There was no maternal mortality. The subsequent deaths of two patients came to our attention later. One died on the fifty-second postpartum day of acute leukemia, and the second died two years after delivery of jaundice of unknown etiology which was present before and during the entire pregnancy.

Infants of Excessive Size.—

There were 30 infants that weighed 4,000 grams or more (Table XIII), an incidence of 18.8 per cent. Our incidence for 1952 was 9.0 per cent. Two of the 30 infants were stillborn. Of the remaining 28 infants, all were in good condition except 2 with fractured clavicles. There were 21 spontaneous deliveries, 3 cesarean sections, 3 midforceps deliveries, 1 assisted breech, 1 breech extraction, and 1 low forceps delivery. Four of these 9 operative cases were in primiparas.

TABLE XIII. INFANTS OF EXCESSIVE SIZE, OVER 4,000 GRAMS. 30 CASES,
INCIDENCE 18.8 PER CENT

	NO. OF CASES
<i>Parity.—</i>	
Multiparas	25
Primiparas	5
Stillbirths	2
Incidental injury	2
<i>Method of Delivery.—</i>	
Spontaneous	21
Cesarean section	3
Midforceps	3
Breech and breech extraction	2
Low forceps	1
<i>Comparative Incidence.—</i>	
Present series	18.8%
New York Lying-In, 1952	9.0%

Patients With Two Pregnancies After 44.—

Four patients appeared twice in this group. Three had term deliveries in both their forty-fourth and forty-sixth years and the fourth had a term delivery followed by an incomplete abortion in her forty-sixth year. All had 4 or 5 children before these last pregnancies occurred.

TABLE XIV. INTERVAL SINCE PRECEDING PREGNANCY

	INTERVAL IN YEARS			
	10-15	15-20	20-25	25 PLUS
<i>Viable Births.—</i>				
Since last child	25	12	7	1
Since last pregnancy	17	13	3	1
<i>Abortions.—</i>				
Since last child	14	15	3	5
Since last pregnancy	10	13	3	3
<i>Incidence of Pregnancy Occurring Ten Years or More After Last Child.—</i>				
New York Lying-In	34.6%			
Chicago Lying-in	18.0%			

Interval Since Preceding Pregnancy.—

It is rather surprising to see the relatively large number who had either a child or an abortion after very long periods of time since the preceding child or abortion (Table XIV). There were several even after twenty years. There were proportionally about twice the number of miscarriages as viable births in

those who had gone over ten years without a pregnancy. The incidence of pregnancy occurring ten or more years after the last child was 34.6 per cent. The incidence of viable birth occurring ten or more years after the last child was 19.0 per cent.

Pregnancy After the Menopause.—

Pregnancy after the natural menopause is most uncommon and documented references are indeed rare. Snaith and Williamson¹⁵ reviewed the literature in 1947 and found but 15 cases. They added a case in which the woman was 45 years of age and had experienced a period of amenorrhea of somewhat over three years before her confinement. In several of the 15 cases, however, the period of amenorrhea before delivery was less than two years.

In 1910 Buckle¹⁶ reported a case of a 50-year-old woman who had a child following eleven years of menopause. After birth she again menstruated regularly for about a year.

The most famous case is one reported by W. J. Kennedy¹⁷ of Edinburgh in 1882 of a term pregnancy at 63 years of age in a *garvida xxiii* who was said to have had five labors and one abortion after the age of 50. The age of this woman, however, was verified only by her statements to Dr. Kennedy and his acquaintance with her for many years.

To better this record we have to go back to 1865 when a Frenchman by the name of Priou¹⁸ described a woman of 72 years of age who had an abortion.

There was no case in our series of 160 deliveries in women over 44 in which there was any period of amenorrhea before pregnancy occurred. In the 77 abortion cases, however, there were 3 where there was some interval of amenorrhea before pregnancy occurred as illustrated in Table XV. The first patient was a woman of 53 years of age who had amenorrhea for two years followed by bleeding and a dilatation and curettage. The pathological report was missed abortion with retained fetal cartilage. The second patient was a woman of 51 years of age who had a period of amenorrhea of eight months followed by one month of bleeding before a curettage was done. The pathological report was retained decidua. The third was 46 years of age with a seven-month period of amenorrhea followed by spotting and a curettage. The pathological report was retained fetal membranes and decidua.

TABLE XV. PREGNANCY AFTER THE MENOPAUSE

	NO. OF CASES	AGES	DURATION OF AMENORRHEA (MONTHS)	SYMPTOMS	PATHOLOGY
Viable Births	0	—	—	—	—
Abortions	3	53	24	Bleeding	Fetal Cartilage
		51	8	Bleeding	Decidua
		46	7	Spotting	Fetal membrane

Perinatal Deaths and Congenitally Abnormal Infants.—

A considerable effort was made to secure a follow-up on the 160 babies of this group, but our percentage of success was only average. Only 61 replies were obtained, primarily because many patients had moved and could not be traced. There were pediatric charts on an additional 20 cases which can be considered an incomplete but fairly reliable follow-up. The only additional information secured beyond that available in the birth records was the discovery of one Mongoloid child that had been called normal at birth. Therefore, we have follow-up reports on about one half of the cases with only one additional abnormality having been found. If this ratio were to hold for the other half of the cases, our present figures would be substantially correct.

There were 18 perinatal deaths. One infant was premature and died on the fifth day, one with a cerebral injury died on the third day, one was a still-born infant with a cerebral hemorrhage, one was stillborn following prolapse of the cord and fetal trauma, and 2 died of undetermined causes in the first hour. An autopsy was performed on one of these last two. Of the other 12 cases 6 were deadborn macerated infants, 3 had congenital anomalies, one was a Mongolian that died in three weeks, one had erythroblastosis, and one with a birth injury died on the sixty-third day of meningitis. There were also 2 other Mongolian infants that survived. The perinatal death rate of 11.3 per 100 births is in contrast to the over-all New York Lying-In perinatal death rate for 1953 of 1.6 per 100 births. Of the 18 infants that died, only 4 were premature.

The 3 infants with congenital anomalies incompatible with life together with the 2 Mongolians that survived and the one Mongolian that died give a total of 6 congenitally abnormal infants, an incidence of 3.75 per cent compared to the over-all New York Lying-In incidence of 0.5 per cent for 1953. Table XVI gives a summary of this information.

TABLE XVI. PERINATAL DEATHS AND ABNORMAL INFANTS

<i>Perinatal Deaths.—</i>	
Normal infants	6
Macerated infants	6
Infants with congenital abnormalities	4
Infant with erythroblastosis	1
Infant with infection—birth injury	1
	18
Incidence per 100 births	11.3%
Over-all incidence per 100 births, New York Lying-In, 1953	1.6%
<i>Congenital Abnormalities.—</i>	
Mongolian	3
Other abnormalities incompatible with life	3
	6
Incidence	3.75%
Over-all incidence, New York Lying-In, 1953	0.5%

Mongolism and Congenital Abnormalities.—

One of the foremost questions in the mind of the elderly gravida concerns the possibility of an abnormal child. What are her chances of having a Mongoloid infant or one with any of a number of congenital defects? What can we tell her as to the causes of these various conditions and what possibilities are there for some degree of prevention? A considerable amount of clinical work and a great deal of experimental work has been done on this subject.

Writing on Mongolism, T. H. Ingalls¹⁹ of Harvard states that this condition is part of the much broader problem of congenital abnormalities in general. "Mongoloids, Siamese twins, monsters, congenital hearts, cleft palates and other similar defects seem related as members of a family of anomalies. The evidence suggests that many anomalous children have survived a period of anoxic distress as others have survived infections, metabolic upsets or nutritional deficiencies.

"Research has demonstrated that environmental factors account for a substantial proportion of all congenital abnormalities and crippling defects. The indications are that every human embryo is a potential candidate for mongolism just as he is for measles, sunburn and auto accident."

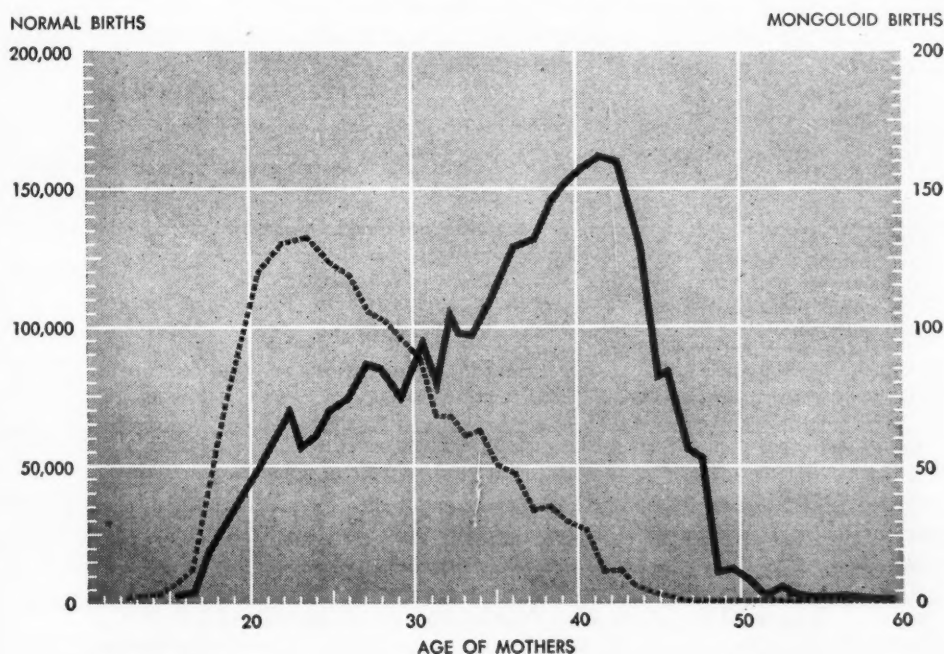
Penrose²⁰ of University College, London, is of the opinion that at present the mode of action of the hereditary background is obscure and much less important, from the point of view of treatment, than the environmental factors de-

pendent upon maternal conditions. J. B. S. Haldane²¹ believes that it is entirely possible that suitable hormone treatment of the elderly gravida could halve the frequency of Mongolism. "Although there is much more to the problem than the use of hormones, present knowledge suggests that the coordinated study of congenital defects will result in a significant contribution to public health."¹⁹

Disastrous to the child of a gravid woman may be an automobile accident,²² elective surgery with anesthesia,²³ infection,²⁴ threatened or induced abortion,²⁵ all of which have been associated with subsequent birth of a Mongoloid child. "Surely the excessive cases of microcephaly and mental retardation following the bombing of Hiroshima²⁶ depend to some extent upon the severe burns, infection, suffocation, hemorrhage and shock to the mothers and are not all due to a single uncomplicated radiation injury."²⁷

TABLE XVII.* MONGOLOID BIRTHS AND NORMAL BIRTHS RELATED TO AGE OF MOTHER

Mothers of mongoloids (solid line, from 2,882 cases) tend to be older than mothers of normal infants (dotted line, from 1934 U. S. births).



*From Bleyer.²⁸

Table XVII from Bleyer²⁸ shows that the peak maternal age in the general population is 24 years whereas in Mongoloid-producing women it is 41 years. Penrose,²⁹ taking figures collected in England and Wales, found that 40 per cent of Mongoloid children are born to mothers over 40 years of age. The risk of birth of a Mongoloid child to women under 30 years of age is about 1 in 2,000 births. The incidence rises rapidly, increasing nearly threefold during each five-year interval and reaching a maximum figure in the late maternal ages of $2\frac{1}{2}$ to 3 per cent. Ingalls¹⁹ states that the incidence of Mongolism is 2 in every 1,000 babies born to mothers in all groups. Vital statistics indicate that, at the age of 40 years and over, 1 per cent of infants born are Mongoloid, and the risk of a second case cannot be ignored in women approaching the menopause.³⁰

There were 3 infants in our small series that showed Mongolism, an incidence of 1 in 53 as against the calculated incidence of about 1 in 35. (A complete infant follow-up predicted on the basis of the present follow-up could produce one added case in all probability which would put our incidence at about that predicted by Penrose.)

Other congenital malformations in their relation to maternal age fall into a similar pattern. Bleyer,³¹ writing on the role of advancing maternal age in causing achondroplasia, of which he collected 303 cases from all over the country, showed a rise in the incidence of achondroplasia with increased maternal age. In the 45 to 49 year age group the incidence was 175 per cent above expectancy. Malpas³² and Murphy³³ showed a positive relationship between the incidence of births of children with malformed nervous systems and increase in maternal age.

A conference on "Parental Age and Characteristics of the Offspring" was held at the New York Academy of Science in January, 1953. A paper presented at that time by D. P. Murphy³³ concluded that after the age of 30 each succeeding five-year period reveals a progressive increase in the proportion of defective children. When birth occurs between 45 and 49 years of age the proportion of defective to normal children was approximately three times as great as when the mothers were under 30 years of age.

TABLE XVIII.* EFFECT OF MATERNAL AGE IN VARIOUS ABNORMALITIES

ABNORMALITY	INFANTS BORN AFTER MOTHER HAD REACHED AGE OF 40 YEARS (PER CENT)
Mongolism	39.5
Chorionepithelioma	33.3
Vesicular mole	33.0
Central placenta previa	17.9
Achondroplasia	13.6
Central nervous system malformation	11.8
Twins of unlike sex	6.3
Anencephaly	5.6
Control populations	3.5 to 5.0

*From Penrose.²⁹

Table XVIII from Penrose²⁹ shows the effect of maternal age in different congenital abnormalities and compares the incidence to that in control populations.

TABLE XIX.* NEONATAL DEATHS RELATED TO MATERNAL AGE

COMPLICATING FACTOR	NEONATAL MORTALITY RATE PER 1,000 LIVE BIRTHS (ALL AGES)	NEONATAL MORTALITY RATE PER 1,000 LIVE BIRTHS (45 AND OVER)
Intracranial hemorrhage	3.5	22.2
Congenital malformations	3.4	4.7
Erythroblastosis	0.6	4.7
Age of the mother	21.5	80.8

*From the Chicago Health Department.⁴³

Table XIX has been compiled from figures taken from the 1951 Annual Report of the Chicago Health Department and reprinted in *Progress in the Prevention of Needless Neonatal Deaths*, by Bundesen, Potter, Fishbein, Bauer, and Plotzke.³⁴ This report covered 18,741 neonatal deaths in 873,310 births over a thirteen-year period. In relation to intracranial hemorrhage the overall neonatal mortality rate per 1,000 births was 3.5 whereas for women over 45

years of age it was 22.2. Congenital malformations did not show any significant difference in the two groups although the number of deaths involved was too small to be of any value statistically. Table XVIII showed great variation in relation to congenital malformations, but these figures included live births and neonatal deaths. Erythroblastosis was eight times as frequent a cause of neonatal death in infants of women 45 years of age and over. Where age alone was the only factor considered, the neonatal mortality rate for women over 45 years of age was four times that for all ages.

Summary

A study of 237 pregnancies in women of 44 years of age and over is taken from 71,827 pregnancies on the New York Lying-In Hospital Service over a twenty-year period. The incidence of pregnancy in this group and the incidence of abortion are shown. The age distribution and outcome of the pregnancy are presented.

Figures on the occurrence of pregnancy after 46 are obtained from six maternity hospitals in addition to those from our series and these are supplemented by the New York City statistics.

A review is made of the primigravid patients appearing in this series, the method of delivery of all patients, and the cesarean sections. In addition, cases of prolonged labor and the indications for operation in the abortions are discussed.

Antenatal complications in relation to the viable births and abortions are presented and compared.

A consideration of maternal mortality, infants of excessive size, patients appearing twice in the series, and those with intervals of ten years or longer since the preceding pregnancy are presented.

A discussion of pregnancy after the menopause is given and those patients in our series who fall into this classification are reported.

Perinatal deaths and congenital abnormalities appearing in our series are reviewed and the high incidence of congenital anomaly presented.

A discussion of the literature on Mongolism and congenital abnormality is given and tables from three different sources to illustrate the relation of these conditions to maternal age are presented.

Conclusions

1. The rate of abortion after 44 years of age is very high, approximately 33 per cent. After 47 years of age abortion occurs in about 80 per cent of the pregnancies.

2. Spontaneous delivery in this elderly age group occurs with an incidence comparable to the over-all service rate. Cesarean section is employed with over twice the usual frequency.

3. Prolonged labor over thirty hours is about ten times as frequent in these cases.

4. Toxemia is three times as common as in the over-all annual incidence, and severe pre-eclampsia occurs nine times as often as in the total pregnancies for the year.

5. The incidence of hydatid mole is over twenty times that usually encountered on the combined obstetrical and gynecological services.

6. Infants of excessive size are twice as common as usual.

7. The incidence of pregnancy occurring ten or more years after the birth of the last child is 35 per cent.

8. The stillbirth and neonatal death rate will be about nine times the over-all annual incidence.

9. The occurrence of Mongolism and congenital abnormalities incompatible with life is about 4 per cent, or approximately eight times the over-all annual incidence.

10. The incidence of viable births after 47 years of age is 1 in 11,000 deliveries.

11. Pregnancy after 50 years of age is exceedingly rare. A viable birth at 50 years of age or over practically never occurs.

12. Pregnancy after the menopause is very uncommon, and a viable birth after the menopause is almost unknown.

I should like to express my appreciation to Dr. R. Gordon Douglas for his kind assistance and many valuable suggestions and to Miss Frances Macdonald of our statistical department for her cooperation in locating these cases and making them available to me.

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Discussion

DR. WILLIAM E. STUDDIFORD.—Dr. Stanton did not tell us how long these patients had been married. Every once in a while you see a woman who has been married for twenty years or more, continuously anxious to have a child, who all of a sudden gets pregnant at 46 or 47. I can remember having the responsibility for such a case twenty years ago. In the patient in question, the membranes ruptured at eight months and I promptly delivered her by cesarean section, thinking this was going to be the only child. About fourteen months later she became pregnant again, and again had to be delivered by cesarean section.

That some multipara went thirty to thirty-five years without becoming pregnant may be a compliment to the efficiency of the contraceptive devices. In the case of the primiparas, however, who suddenly became pregnant at 40 to 45, I would like to know how long they were married and what the period of sterility was.

DR. ANTHONY D'ESOPPO.—I would like to call attention to one of the mistakes we make in medicine very frequently, that is, the comparison of a great many cases that have a great many dissimilar points about them. A woman who has had her first baby at 45 is certainly an entirely different individual from a woman of 45 who has already had one or more babies.

As I see the problem of the primipara of 45, she is so anxious to have this baby and the obstetrician is so anxious to deliver this baby successfully and safely, that cesarean section is frequently done. The woman in the middle parity group usually does pretty well. She usually has very few obstetrical complications. On the other hand, the older woman who has had many babies is very frequently beset with many of the problems we see, placenta previa, erythroblastosis, uterine inertia, malposition, so that these individuals vary a great deal and are not statistically comparable.

There is probably no question that congenital anomalies and toxemia of pregnancy and hydatid moles occur in the older obstetrical group irrespective of parity, but I think the paper would have made a great deal more sense if Dr. Stanton had broken down his series into the degree of parity for the entire group.

DR. CURTIS L. MENDELSON.—We look somewhat askance at patients who have had a labor of thirty hours or more in this elderly age group, especially the primiparas.

Most of these labors of over thirty hours' duration date back to the earlier part of the series, about 1932, when cesarean section was not being employed so frequently.

DR. CARL T. JAVERT.—Dr. Stanton made reference to a number of abortions in women with the symptoms of menometrorrhagia, and I question the advisability of including such cases in his particular study. These cases obviously represent mistakes on the part of the physician who was probably dealing with a threatened abortion which he misdiagnosed and carried to completion. So perhaps those 24 cases should be eliminated from the cases of spontaneous abortion, inasmuch as they represent in effect unintentional abortions.

In the time covered by Dr. Stanton's study, we have had to date some 90 unintentional abortions in our institution, which represents a small fetal loss in terms of undiagnosed pregnancies, especially in connection with myomas of the uterus or incidental to plastic repair. I wonder if, by removing such cases, Dr. Stanton might have a much lower incidence of abortion in this elderly group.

DR. GEORGE L. BOWEN.—I think all of us are confronted with the question from an elderly patient whether she would be safe to discard the diaphragm. My rule has been to tell a patient that after a year of amenorrhea she is probably safe.

I wonder if in going over these data Dr. Stanton found any of these women who had had amenorrhea of this duration, and nevertheless became pregnant.

DR. WILLARD G. FRENCH.—I would like to ask Dr. Stanton if he would comment further on the incidence of hydatid mole. I was shocked to have such a case in a woman of 51, who had had a little indiscriminate bleeding, with a negative Friedman test. I curetted her and to my amazement recovered typical grapelike vesicles. I thought this extraordinary at the age of 51, with a negative Friedman test, but the histologic diagnosis proved to be benign hydatid mole.

DR. STANTON (Closing).—I do not know how long the primiparas were married before they had their children or made their attempt to have children. It might have been possible but I do not think I could have obtained the information in all cases.

Dr. Javert mentioned 24 menometrorrhagia cases which he suggested might be excluded and the incidence of abortion thereby reduced. As these were pregnancy cases, although they were not originally diagnosed as pregnancy, but were diagnosed or discovered by pathological examination, they were justifiably included as pregnancies.

In regard to Dr. French's question about the hydatid moles, none of them apparently became malignant as far as any of our records show. They were all recorded as early moles and all discovered in the abortion cases. The diagnosis was usually a pathological one and not made from the clinical finding.

There were some pregnancies after the apparent menopause, but this was a rather rare situation. Snaith and Williamson reviewed the literature some time ago and found a handful of cases, only 15. They added one other of a woman of 45 who had amenorrhea for three years and then had a child.

There were 3 patients who had abortions after periods of amenorrhea. One was 53 years old, had had amenorrhea for two years before she began to bleed again and had a curettage, and was found to have had an early pregnancy. A second was a 51-year-old woman who had eight months of amenorrhea and then had an early abortion. The third was a 46-year-old woman who had gone seven months without a period and then had spotting and a curettage.

THE TREATMENT OF HYPEREMESIS GRAVIDARUM WITH CHLORPROMAZINE*

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THE purpose of this paper is to report the experience at Sloane Hospital in the treatment of hyperemesis gravidarum with chlorpromazine (Thorazine; 10 -[3-dimethylaminopropyl] -2-chlorophenothiazine).

Material

Between February 1, 1954, and Aug. 31, 1955, a period of 19 months, all patients with hyperemesis gravidarum at Sloane Hospital were treated with chlorpromazine. This series includes 40 patients who were treated at Sloane Hospital only, and two patients who were treated with chlorpromazine elsewhere and were then referred to Sloane Hospital. One of the latter two patients was then re-treated with chlorpromazine at Sloane Hospital.

Eleven of these 42 patients were primiparas, 31 were multiparas; 29 were ward patients, and 13 were private. Of the 29 ward patients, 14 were Negro and 5 Puerto Rican. The age range was 16 to 38 years.

The hyperemesis was classified as markedly severe in 37 cases, moderately severe in 5. In 21 of the 29 cases tested, the urinary acetone was 4 plus, in the remainder it was 2 plus or 3 plus. The weight loss was 10 pounds or more in 18 patients, 3 to 9 pounds in 9 patients, and unknown in 15. Among the 31 multiparas, 21 had experienced severe hyperemesis with their previous pregnancies, 9 moderately severe, and 1 unknown. Twenty-nine of the 42 had had prior therapy to no avail with one or more other drugs (Dramamine, Bonamine, pyridoxine, phenobarbital, etc.) before chlorpromazine was used.

Thirty-five of the 42 patients first received chlorpromazine in the first trimester of pregnancy, 5 in the second (14, 14, 15, 16, and 19 weeks), and 2 in the third. One of these latter was thought to represent hyperemesis tardum; the other had vomited intermittently throughout her pregnancy, more severely in the last trimester.

As for the duration of symptoms before chlorpromazine therapy, 9 had been vomiting severely for one week or less, 7 for 2 weeks, 4 for 3 weeks, 8 for 4 weeks, and 14 for more than 4 weeks.

Method of Treatment

Twenty-eight of the 42 patients were started on chlorpromazine while in the hospital, 5 received the drug first as outpatients and then in the hospital, and 9 were treated as outpatients only. Seven had had previous hospitalizations during the same pregnancy for antiemetic treatment with other drugs, with variable results.

Initial Treatment.—Of the 33 patients who received chlorpromazine in the hospital, all but 4 were given initial infusions of dextrose in water and dextrose in saline, 2,000 c.c. or more. Twenty-six were started on a regular diet; visitors were permitted and the patients were allowed out of bed. The

*The chlorpromazine used in this study was supplied as Thorazine by Smith, Kline & French Laboratories, Philadelphia, Pa.

initial dose of chlorpromazine was given intramuscularly in 29 cases (25 received 50 mg., 3 received 25 mg., and 1 received 100 mg.). Two were started on 25 mg. by mouth, and 2 on 50 mg. by mouth.

Maintenance Dose.—It was quickly discovered that the maintenance dose of chlorpromazine varied considerably from individual to individual. After the initial dose just described, which was usually given intramuscularly, 25 of the patients were started on 50 mg. three times a day by mouth, 13 on 25 mg. t.i.d., and 3 on 10 mg. t.i.d. If the response to the initial dose was found after a few days to be adequate, it was then reduced, e.g., from 50 mg. t.i.d. to 25 mg. t.i.d. or from 25 mg. t.i.d. to 10 mg. t.i.d. The ideal maintenance dose was found to differ from patient to patient and individualization of dosage was, therefore, required to achieve the ideal balance of therapeutic and toxic effects. The minimum effective dose was found to be 25 mg. t.i.d. in 26 patients, 50 mg. t.i.d. in 7, and 10 mg. t.i.d. in 5.

Outpatient Treatment.—The patients were usually kept in the hospital during this period of dosage adjustment, then discharged on whatever seemed to be the ideal dosage for each patient, to continue therapy at home. Of the 33 patients who received chlorpromazine in the hospital, 15 were discharged on a maintenance dose of 25 mg. t.i.d. 3 on 50 mg. t.i.d., and 3 on 10 mg. t.i.d. The duration of hospitalization varied from 4 to 54 days; 10 required subsequent hospitalizations for chlorpromazine therapy, one patient as many as four times. While in the hospital, the duration of the chlorpromazine therapy averaged 12.1 days per patient. While some of this time was spent adjusting the individual dosage, much of it was therapeutically unnecessary and was used for the performance of the placebo and withdrawal tests described below. Following discharge, 22 patients were maintained on chlorpromazine at home for 1 to 20 weeks. The total duration of hospital and outpatient chlorpromazine therapy ranged between 2 days and 24 weeks; the average was 5 weeks. Four patients required chlorpromazine for longer than 10 weeks, 7 for 7 to 10 weeks, 9 for 4 to 7 weeks, 22 for less than one month. Several of the patients seemed to become "addicted" to the drug in that they felt they must have it until well beyond the probable duration of their disease.

Time and Route.—The time of administration was routinely three times daily, one-half hour before meals. Fifteen of the 33 patients observed in the hospital were found to need their initial morning dose immediately upon arising. The route of administration, after the initial dose, was always by mouth. One patient was found to respond only to the intramuscular route. Other antiemetics were never prescribed after chlorpromazine treatment had been started.

Placebo Test.—After chlorpromazine had been administered for sufficient time—usually two or three days—to be thoroughly effective, placebos were substituted in 14 patients; these placebos were identical in taste and appearance to the actual drug and were supplied by the same laboratories. They were administered in the same way as the drug. Twelve of these 14 patients began to vomit furiously 24 to 48 hours after the substitution; they were then replaced on the drug and the vomiting promptly ceased. Two patients who had been cured by the chlorpromazine failed to vomit when the placebos were given in place of the drug.

Withdrawal Tests.—After they had been cured by chlorpromazine, the sudden withdrawal of the drug precipitated a recurrence of hyperemesis in 14 patients. The others could be deprived of the drug, after they had been cured, without recurrent vomiting, but this was usually effected by tapering the dose after the vomiting had passed.

Results of Therapy

Among the 42 patients treated, 30 were regarded as completely cured, 5 as improved, and 7 as unrelieved. Of the 7 who were "unrelieved," 4 did not

respond to their only course of treatment; 2 failed to respond to a first course, but did respond to a second; one responded well initially but ultimately vomited on increasing doses of the drug, which was finally discontinued. Five of the 7 failures occurred among the 14 patients whose treatment was begun on an outpatient basis. Only 2 of the 28 patients whose treatment was begun in the hospital ultimately failed to respond, and one of these failures occurred after the patient had been discharged from the hospital.

Most of the patients responded to chlorpromazine therapy immediately. Despite the severity of their disease, 19 of them never vomited again after the first dose of the drug. Eleven vomited only during the day or two required to determine the correct individual dose. Eight of the remaining 12 vomited at home taking the drug; 4 of these ultimately failed to respond. Only 4 of the 33 patients hospitalized vomited while taking the drug following dosage adjustment, and only one of these ultimately failed to respond.

Toxicity

During chlorpromazine therapy, at least 32 of the 42 patients complained of feeling sleepy, dizzy, and/or weak. Several of these patients fell on the floor of the ward. No episodes of true syncope or severe hypotension were noted. Aside from one patient who received one intramuscular injection of 100 mg., and one other patient who received 75 mg. t.i.d. for one day, no one was given more than 50 mg. t.i.d. The most marked symptoms of lethargy and asthenia were observed with this latter dosage. These symptoms were counteracted in most cases by reduction in dosage and/or the concomitant administration of Dexedrine sulfate, 5 mg. t.i.d. Only 7 patients were entirely free of toxic symptoms, and 4 of these never received a dose of chlorpromazine greater than 25 mg. t.i.d.

During chlorpromazine therapy, one patient developed unexplained hematuria; 2 patients developed evanescent fevers, one attributed to sinusitis and the other to pyelitis. Although these three complications were never thoroughly explained, it is doubtful that they were related to the chlorpromazine.

As for the effect of the therapy on fetal outcome, 24 of the 42 patients have had normal term births, 12 have not yet delivered, one was delivered of a living 30 week premature child, and 2 were not followed. There was one spontaneous abortion at 3 months, one therapeutic abortion at 2 months, and one fetal death in utero at 30 weeks associated with severe hypertensive cardiovascular disease and superimposed pre-eclampsia. There is no reason to believe that chlorpromazine had an adverse effect on any of these pregnancies.

Six of the 42 patients developed icterus. Two of these patients were referred to Sloane Hospital with icterus following treatment with chlorpromazine elsewhere. The incidence of icterus among the 40 patients originally treated at Sloane Hospital was, therefore, 4 among 40, or 10 per cent.

The fact that chlorpromazine can cause icterus is now indisputable. Forty-three cases have been reported in the literature reviewed.¹⁻¹⁰ An analysis of 7 articles¹⁻⁷ in which the incidence is cited reveals that among 2,847 (mostly psychiatric) patients treated with chlorpromazine, 36, or 1.3 per cent, became jaundiced. The reported incidence seems to be rising slightly as the syndrome is becoming more widely known.

The literature on chlorpromazine therapy of hyperemesis gravidarum is as yet quite small. Benaron and associates¹¹ treated 17 cases of hyperemesis and did not observe any jaundice. Moyer and his co-workers,² treating 3 other pregnant women, likewise failed to detect any biliary pathology. Other reports,^{13, 14} dealing with the use of chlorpromazine in labor, do not mention this complication. It remains to be seen, however, whether pregnancy, and particularly hyperemesis gravidarum, predisposes to the development of icterus.

The pathologic basis of "chlorpromazine jaundice" is known to be similar to that sometimes caused by arsphenamine.¹⁵ It is a pericholangiolitic lesion associated with precipitation of inspissated bile in the finer biliary radicles within the liver, causing a secondary obstructive type of jaundice without concomitant liver-cell damage. (Liver biopsy in one of our cases revealed the same changes.) In the cases encountered thus far, the jaundice is self-limited and, so far as is known, there is no residual damage to hepatic or biliary systems. The jaundice is associated with hyperbilirubinemia (5 to 10 mg. per cent in our series), bilirubinuria, elevated alkaline phosphatase (10 to 20 Bodansky units per cent in our series), negative cephalin flocculation and thymol turbidity, normal cholesterol esterification, normal prothrombin time, and a transitory eosinophilia (10 to 25 per cent in our series). The icterus is usually accompanied by pruritus and preceded by the observation of dark urine, light stools, and tenderness in the liver area.

The mechanism of chlorpromazine jaundice is obscure. Analysis of our results suggests that *dehydration* may play a role in the precipitation of the bile pigment. All 6 of our cases of jaundice developed in women whose hyperemesis did not respond to the drug, i.e., who continued to vomit severely while taking chlorpromazine. Of the 7 patients who failed to respond to the drug, 6 became jaundiced; of the 35 who responded, none became jaundiced.

Dehydration is obviously not the only factor involved. As previously noted, jaundice is seen among psychiatric patients treated with the same drug; and I have observed one case of jaundice among 17 patients treated for menopausal symptoms with small doses of chlorpromazine. But if this complication occurs more frequently in the treatment of hyperemesis, perhaps dehydration is part of the explanation.

Closely linked to the dehydration theory is the fact that all 6 of the cases of chlorpromazine jaundice developed in patients who were receiving the drug on an outpatient basis. As pointed out before, response to the drug was considerably enhanced by hospitalization. Five of the 6 cases of jaundice were in private patients, for whom hospitalization is so reluctantly advised. Among the 13 private patients in this series, only 4 were hospitalized for chlorpromazine therapy; none of these 4 developed jaundice in the hospital, but one became jaundiced after taking the drug at home for 10 days. The remaining 9 patients were treated with chlorpromazine as outpatients only, and 4 of them developed jaundice. Of the 4 ward patients who received chlorpromazine initially as outpatients, one became jaundiced; none of the 25 ward patients whose treatment began in the hospital became jaundiced.

Total Dosage and Duration of Therapy.—Regardless of the dose of the drug, if jaundice is going to develop, it will almost surely do so within the first 3 weeks of therapy. It is interesting to note that the only patient in whom chlorpromazine was a failure and who did not become jaundiced had responded to the drug during the first 4 weeks of her treatment. Some patients in this series received chlorpromazine for as long as 24 weeks, with a total dosage as high as 12,750 mg. without developing jaundice. The patients who did develop jaundice received total doses of only 500 to 3,150 mg. over a period of 4 days to 3 weeks.*

Another hypothesis which bears investigating is the possibility that these patients who develop chlorpromazine jaundice have in their backgrounds some *predisposing disease* of the gall bladder and/or biliary tree. It may be significant that one of the patients who had jaundice in this series had had a cholecystectomy for stones and jaundice 6 months previously and another had gall

*Since this paper was submitted for publication, another case of chlorpromazine jaundice has occurred in a patient with hyperemesis 2 weeks after a single 50 mg. injection of the drug.

stones demonstrable by x-ray at the time of treatment. No such findings were noted in the other 4 cases, however, and one had a negative gall bladder series.

Perhaps the factor of *bile stasis*, generally thought to accompany pregnancy, might help to explain a higher incidence of chlorpromazine jaundice among gravid women.

An *allergic basis* has been proposed.^{3, 6, 8} The eosinophilia would, of course, tend to support this explanation. Allergic dermatitis had been reported due to consumption and handling of the drug. Perhaps failure of vomiting to respond to the drug is, in itself, an allergic manifestation and may serve as a warning that jaundice may ensue. Popular as this allergic allegation has recently become, however, it seems to me the least tenable, as I find it difficult to conceive that any drug can cause an allergic reaction which is manifested principally through the biliary system.

It is doubtful that any one of these theories will ultimately prove to be the sole explanation for all cases of chlorpromazine jaundice. It seems most likely, at this point, that several of these factors play contributory roles, and that some of them are aggravated by the pregnant state.

Other toxic reactions which have been attributed to chlorpromazine, such as agranulocytosis,⁹ were not seen in this series.

The *clinical course* in the 6 cases of chlorpromazine jaundice was uniformly mild. The jaundice disappeared in all cases within a week, and all laboratory tests were normal within 2 to 3 weeks. Treatment consisted simply of rest and hydration. The first case of icterus occurred in a private patient who had concomitant pyelitis and a history of cholecystectomy 6 months previously. The picture at that time—before the syndrome of chlorpromazine jaundice was generally known—was so confusing that a therapeutic abortion was performed. After the relative harmlessness of the disease became established, 2 of the patients with chlorpromazine jaundice were replaced on the drug as soon as the liver chemistry determinations reverted to normal. Whereas neither of these patients had responded to the drug as outpatients before the jaundice, they both responded well to the second course of therapy started in the hospital. One of them became so "addicted" to the drug that she continued to take it for the remaining 6 months of her pregnancy, without further ill effects.

Aside from the 6 cases of chlorpromazine jaundice, the serum bilirubin was determined in 14 other patients who did not exhibit icterus and was found to be transiently elevated to 4.1 mg. per cent in one case. Similar studies by other authors^{3, 4, 7} also suggest a certain incidence of subclinical biliary damage, and it has been wisely proposed that all patients on chlorpromazine therapy have biweekly urinalyses for bile.

Comment

In my opinion, hyperemesis gravidarum is a psychogenic disease which is triggered by the hormonal changes of pregnancy. That previous drugs, with peripheral actions, have failed to cure this disease is not, from this point of view, surprising. It seems more logical to use a drug with central action upon both the emetic and psychic centers. Chlorpromazine is the first such important drug available to us. It is not surprising, therefore, that this new drug is so effective in the treatment of this disease.

The main drawback to the treatment of hyperemesis with chlorpromazine is its toxicity. Whether hyperemesis and/or pregnancy actually tend to increase the incidence of this toxicity remains to be seen. This small series might, meanwhile, serve as a warning of such a possibility.

Since chlorpromazine therapy for this disease seems to be more effective when initiated in the hospital and since jaundice seems to occur less often in patients who respond well to the drug, it seems almost mandatory that initial chlorpromazine treatment be administered on a hospital basis.

All reports to date indicate that the course of chlorpromazine jaundice is mild and self-limited. It is a complication which is nonetheless extremely undesirable. It need hardly be emphasized that even a 1 per cent risk of this complication precludes the use of chlorpromazine in the treatment of the milder forms of pregnancy nausea and vomiting. One death has already been reported from chlorpromazine jaundice in a patient with previous liver disease,⁶ and several authors^{4, 6, 7} have reported cases in which the jaundice has persisted for longer than 6 months.

It is to be hoped, therefore, that these toxic reactions can be avoided in the future or that new drugs, similar in action to chlorpromazine, will be found without these hazards.

Summary

1. The results of the treatment of 42 cases of hyperemesis gravidarum with chlorpromazine are presented.

2. The severity of these cases is documented by the incidence of acetouria, weight loss, history of hyperemesis with prior pregnancies, and failure to respond to other drugs during the current pregnancy.

3. The dosage regimen is outlined, emphasizing the importance of beginning therapy in the hospital and individualizing the dose according to the patient's response.

4. Thirty of our 42 patients were cured, 5 were improved, and 7 were initially unrelieved. Two of the latter 7 responded to a second course of therapy.

5. The toxicity of the drug is discussed in detail. All but 7 of the 42 patients exhibited some degree of toxic reaction, usually somnolence and weakness. Four of our own patients became jaundiced, an incidence of 10 per cent. Two other cases of jaundice were sent to us, and one other patient had a transient elevation of serum bilirubin.

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A DISCUSSION OF THE PROPER PLACE OF SURGICAL INDUCTION WITH A REVIEW OF ITS HAZARDS*

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INDUCTION of premature labor was first introduced by Macauley in 1756 as a treatment for cases of contracted pelvis; he employed rupture of the membranes. Since his time surgical induction has been used extensively and alternative methods have been employed. In my own hospital, Guy's, surgical induction has found a good deal of favor and the senior registrar and chief assistant in the department, Evans,¹ has recently reviewed in the *Lancet* 843 cases performed between 1928, the year when we commenced to publish annual reports, and 1952. During this time 25,960 mothers were delivered, so the incidence of induction is 3.3 per cent. Surgical induction is undertaken only for strict indications such as pre-eclamptic toxemia, disproportion, and postmaturity, and has not been performed simply because the patient has reached term (Table I). A subsequent breaking down of the figures into five-year periods has shown a remarkable uniformity of results between each of these.

TABLE I.* INDICATIONS FOR INDUCTION

INDICATIONS	NO. OF CASES	PER CENT
Pre-eclamptic toxemia, essential hypertension, and chronic nephritis	446	52.8
Disproportion	215	25.5
Postmaturity	85	10.2
Others	97	11.5
Total	843	100.0

*Tables I-VII and IX, Guy's Hospital Figures: Evans, G. M.¹

TABLE II. METHODS OF INDUCTION

METHOD OF INDUCTION	NO. OF CASES	PER CENT OF TOTAL INCIDENCE
Rupture of membranes	507	59.0
Low rupture	155	18.0
High rupture	153	17.8
Site not specified	199	23.2
Stomach tube (rubber bougie)	184	21.3
Animal bladder	159	18.5
Krause bougie	9	1.0
Digital separation of membranes	2	0.2
Total	861	100.0

It has been recognized by all that surgical induction carries risks to mother and baby, and these risks have to be assessed in each case against the risks of doing nothing or alternatively performing cesarean section. It

*Presented at a meeting of the New York Obstetrical Society, Nov. 9, 1954.

might be that one method of induction is safer than another and/or more efficient, and one of the reasons for Evans undertaking this review was my repeated assertion that I believed that induction with a tube was more efficient and no more dangerous in cases of disproportion. I should explain that induction for disproportion for many years has been undertaken only to avoid the repetition of a previous difficult forceps delivery.

Table II shows the different methods of induction used.

Maternal Mortality

Of the 843 mothers, I was surprised to find that 7 had died, but 4 of the deaths I think should not be attributed to induction. One mother died from postpartum hemorrhage, one from fulminating eclampsia, and two from pulmonary embolism without evidence of birth-canal infection. The death of the other three must be attributed to the inductions (a rate of 3.6 per thousand). During this period of 1928 to 1952 the over-all maternal mortality for the Department was 2.4 per thousand, including all emergencies (1.7 for 20,558 cases from our own area).

The first patient to die was a gravida ii, aged 41, with a history of a difficult forceps delivery due to disproportion. Labor was induced at 38 weeks by high rupture of the membranes with a Drew-Smythe catheter. She had a partial placenta previa and severe bleeding was caused. The obstetrician performed a cesarean section and delivered a dead baby. The mother died from hemorrhage and shock.

Labor was induced in the second patient, a primigravida, for hydramnios by rupture of the forewaters. She was delivered within 24 hours and had a fever on the day of delivery. She developed paralytic ileus and died on the twelfth day from perforation of the cecum. *Escherichia coli* was cultured from the birth canal terminally, but there was no other evidence of birth-canal infection.

Labor was induced in the third patient, a primigravida, by rupture of the hindwaters at 32 weeks. She had a severe pre-eclamptic toxemia. Labor did not start and 80 hours later a tube was introduced; labor commenced shortly after this and she was delivered of twins. She became febrile and culture of the lochia showed *Pseudomonas pyocyanea*. She died six weeks later from infective endocarditis due to this organism. All 3 deaths have occurred since 1937.

You may think that the two deaths from embolism should also be included, as possibly due to low-grade infection.

Maternal Morbidity

Maternal morbidity is judged by a standard of puerperal pyrexia of 100.4° F. or over, maintained for 24 hours or recurring within that period during the first 21 days of the puerperium. Table III shows the over-all incidence to be 10.8 per cent as against 4.3 per cent for spontaneous labors.

Infection of the birth canal occurred in 5.3 per cent of cases and shows little variation according to what method was used. Urinary tract infection was also increased to 4.0 per cent; it was 1.2 per cent in noninduction cases.

The longer the induction-delivery interval, the greater the morbidity. Of those delivered within 48 hours, only 6.6 per cent showed pyrexia of the above standard, while 15.3 per cent of those delivered in 48 to 96 hours developed pyrexia, and 20.7 per cent of those who took longer than 96 hours to be delivered. Of those delivered within 48 hours, infection of the birth canal occurred in 3 per cent, and of those delivered after 96 hours infection

occurred in 11.5 per cent. Antibiotics were seldom used. I think I am right in saying that Eastman in a paper given in London last year showed that penicillin, anyhow, was of little use as prophylactic treatment in such cases, and this has been our experience. Other antibiotics I cannot at present assess in this connection.

The risks to the mother are not negligible, it is quite clear. I have as yet little experience of induction using the Pitocin drip, and in the light of what experience I have I still feel a little hesitant to use it in pre-eclamptic toxemia or postmaturity on account of increasing the risk of anoxia in the fetus, when the placenta may already be insufficient. Nor would I like to use it in disproportion.

TABLE III. MORBIDITY ACCORDING TO TYPE OF INDUCTION

METHOD OF INDUCTION	NO. OF CASES	MORBID		GENITAL INFECTION	
		NO.	PER CENT	NO.	PER CENT
Rupture of membranes	507	55	10.8	31	6.1
Low rupture	155	17	11.0	9	5.8
High rupture	153	21	13.7	12	7.8
Site not specified	199	17	8.5	10	5.0
Stomach tube (rubber bougie)	184	15	8.2	8	4.3
Animal bladder	159	19	11.9	5	3.1
Krause bougie	9	2	22.2	1	11.1
Digital separation of membranes	2	—	—	—	—
Total	861	91	10.8	45	5.3

Fetal and Neonatal Deaths

The next two tables (Tables IV and V) show an analysis of the causes of stillbirths and neonatal deaths, which together totaled 135 out of 867 infants delivered, an over-all loss of 15.6 per cent. There was almost no difference between multiparas and primigravidas.

TABLE IV. CAUSES OF STILLBIRTHS

Intracranial hemorrhage due to dystocia	12
Toxemia, hypertension, and nephritis	32
Congenital malformations	17
Diabetes and Rhesus incompatibility	2
Anoxia following accidental hemorrhage due to induction	2
Intrauterine infection	3
Prolapsed cord	12
Unknown	22
Total	102

TABLE V. CAUSES OF NEONATAL DEATHS

Intracranial hemorrhage	9
Prematurity	11
Congenital malformations	2
Atelectasis	7
Rhesus incompatibility	2
Pneumonia	1
Meningitis	1
Total	33

The next table (Table VI) shows the incidence of attributable stillbirths, i.e., stillbirths due to toxemia, malformations, etc., are excluded; there is little difference between the various methods used and the rate works out

at 2.1 per cent. The attributable stillbirth rate was not influenced by the length of the induction-delivery interval as judged by a comparison of those cases delivered within 48 hours and those delivered after 48 hours.

TABLE VI. METHOD OF INDUCTION AND STILLBIRTH RATE

METHOD OF INDUCTION	TOTAL STILLBIRTHS (PER CENT)	ATTRIBUTABLE STILLBIRTHS (PER CENT)
Rupture of membranes	11.6	2.2
Low rupture	20.0	2.6
High rupture	9.8	2.6
Site not specified	6.5	1.6
Stomach tube (rubber bougie)	9.9	2.2
Animal bladder	14.5	1.9
Krause bougie	22.2	—
Total	11.8	2.1

Prolapse of the Cord

I now want to turn to prolapse of the cord: Where surgical induction was considered the cause of fetal death, it was by far the commonest cause. This complication occurred 27 times, an incidence of 3.2 per cent. This is higher than that in the series reported by Bannister,² 1.6 per cent in 745 inductions, or by Plass and Siebert,³ 1 per cent incidence. Thirteen babies were born alive, and 14 were stillborn; of these, 2 were dead from toxemia before the cord prolapsed, and in a case of breech, where the cord was replaced successfully, the baby was stillborn as a result of intracranial hemorrhage. There were therefore 11 stillbirths due to prolapse of the cord. These figures no doubt could be improved with the greater readiness in recent years to do cesarean section for this condition.

The type of induction did not seem to affect the incidence of prolapse of the cord (Table VII), but the incidence in multigravidas (4.1 per cent) was more than double that in primigravidas (1.8 per cent). This I attribute to the greater frequency of nonengagement of the head in multigravidas. In all cases of prolapse of the cord, the fact of engagement or nonengagement is recorded in the notes; in 239 cases in which the head was engaged there were 6 prolapsed cords, and in 289 cases with nonengagement of the head there were 21 prolapsed cords. In the other 315 cases there was no reference in the notes to engagement or nonengagement of the head but there was no case of prolapsed cord. If one may assume, however, that the head in these cases was engaged or not engaged in the proportion of 239:289 (the figures I have just given), the incidence of prolapsed cord is 1.6 per cent when the head was engaged and 4.6 per cent when it was not.

TABLE VII. METHOD OF INDUCTION AND PROLAPSE OF CORD

METHOD OF INDUCTION	NO. OF CASES	PROLAPSED CORD NO. OF CASES	INCIDENCE PER CENT
Rupture of membranes	507	16	3.2
Low rupture	155	6	3.9
High rupture	153	7	4.6
Site not specified	199	3	1.5
Stomach tube (rubber bougie)	184	6	3.3
Animal bladder	159	5	3.1
Total	850	27	3.2

Clearly, prolapse of the cord is a very considerable risk when induction is performed with the head above the brim, and it should not be considered

under these circumstances unless the risk to the child is greater than 2.5 per cent (assuming only half the babies are lost), or because there is some definite danger to the mother in letting pregnancy proceed, and it seems to me that cesarean section should often be undertaken as an alternative.

Indications for Induction of Labor

Ideally, for a successful induction the head should be well engaged and the cervix soft and partially effaced, and the patient should be at term or a little past; many workers have reported series of cases of elective induction achieved with great safety when these criteria were observed; even so I have three times seen babies with *Esch. coli* meningitis following rupture of the membranes at or past term and I do not believe this procedure is entirely free of risk to the child even under these favorable conditions. The real problem, however, is whether one should do induction of labor before term in pre-eclamptic toxemia and in disproportion, and whether one should induce labor for postmaturity, or whether one should resort to cesarean section more freely.

Speaking generally, I am loth to do a cesarean on a woman who can be delivered vaginally with safety except when there is actual evidence of serious fetal distress or unless she is a primigravida of over 35 years.

Postmaturity.—

I think it is easiest to consider postmaturity first. There has been much argument in Great Britain as to the risks of postmaturity, if any, but some of us have been convinced for a good many years that there was an increasing risk of anoxia of the fetus in utero after term had been passed, and that the risk of intrauterine death or unexpected death in labor became considerable somewhere about 43 weeks, and now James Walker⁴ in his Blair-Bell Memorial lecture, published this year, has given us an excellent study in support of this belief. He has measured the oxygen in the cord blood before the onset of labor and at the moment of birth at 40, 41, 42, and 43 weeks, and he finds that 30 per cent saturation (50 to 60 per cent is the normal) is the "distress level," and that this is signalized by the passage of meconium; at this level he shows that the blood in the umbilical artery is almost devoid of oxygen. At 40 weeks most fetuses are well oxygenated and have a good reserve, but the oxygen supply falls rapidly after 40 weeks and by 43 weeks many are down to 30 per cent saturation and have reached the "distress level" even before labor starts, with resultant death in utero, or early distress in labor, and sometimes death during labor with very little warning indeed.

James Walker states that in Aberdeen 21 per cent of all primigravidas are delivered after the forty-first week. In this 21 per cent there are to be found the following:

- 51 per cent of all unexplained deaths (mature),
- 83 per cent of all deaths from anoxia in difficult labor,
- 40 per cent of all deaths from trauma in difficult labor,
- 36 per cent of all cesarean sections for difficult labor.

He considers that the main problem is in primigravidas over 25 years of age.

He uses the term "obstetric death" to cover all stillbirths and all neonatal deaths in the first week of life; such deaths with rare exceptions arise from causes present during pregnancy or labor. He shows that the obstetric death rate at 40, 41, 42, and 43 weeks is 1.5, 1.2, 2.1, and 3.9 per cent, respectively, while at 44 weeks it is as high as 6.5 per cent. He finds that anoxia plays the main part in this rise, either directly or indirectly.

Rathburn⁵ gave the stillbirth rate for postmaturity as 5.2 per cent and Clayton⁶ as 6.15 per cent. Both were considering deliveries after 42 weeks. Clifford⁷ of Boston gives a figure of 12 per cent for deliveries after 300 days. Walker thinks his own figures are rather lower because they have so many young primigravidas—under 25 years—in Aberdeen.

Clearly it becomes worth while to accept the 1.6 per cent risk of prolapsed cord in a primigravida with the head engaged at 42 weeks (Walker would say at 41 weeks), and to perform induction of labor; but it is worth while to induce labor in a multigravida with the head above the brim? On the over-all Guy's figures (4.6 per cent prolapsed cord) it is not, unless possibly one stands by ready to do a cesarean section on very short notice should the cord prolapse. It is possible, however, that in the absence of disproportion the risk of prolapsed cord is less, but I have not enough cases to know.

Table VIII from Walker's lecture gives the Aberdeen figures for induction in primigravidas at 41 weeks or soon after, by rupture of the membranes. They show a very striking fall in fetal loss since adopting this policy. In 1948, Walker writes me, 9 out of a total of 31 obstetric deaths for the year occurred in babies born more than two weeks past term, and, as he says in his letter, "the over-all obstetric death rate in primigravidae can be dropped 4 to 5 per 1,000" by induction, at 41 weeks he would say, but I have usually waited until 42 weeks.

TABLE VIII.* OBSTETRIC DEATH RATE AFTER THE END OF THE FORTY-FIRST WEEK OF PREGNANCY IN PRIMIGRAVIDAS

YEARS	NO. OF CASES	OBSTETRIC DEATHS	RATE PER 1,000
1948 - 1949	400	14	35.0
1950 - 1951	359	7	19.5
1952 - June 1953	259	4	15.4
January to June, 1953	91	1	11.0

*From James Walker.⁴

Disproportion.—

Turning now to disproportion, what are the risks to the baby? In the Guy's series there were 215 inductions for disproportion, 163 in multiparas and 52 in primiparas (almost all the latter done in the early years in this series); there was a total fetal loss, "obstetric deaths" to use Walker's term, in this series of 28. If 5 breech deliveries are excluded, this is a rate of 11 per cent; there were 7 stillbirths from prolapsed cord, and 4 babies lost from intracranial hemorrhage. It is interesting that there were in all 11 prolapsed cords, 10 of them in multiparas, an incidence of 6.4 per cent in the latter group, a very high figure.

Table IX shows the methods of induction. The stomach tube was no more efficient than rupture of the membranes in cases of disproportion, and it appears that artificial rupture of the membranes comes out worst; but any form of surgical induction is poor treatment, and I rather regretfully come to the conclusion that surgical induction of labor even in multiparas is not ordinarily the treatment of choice now that the risks of cesarean section are so small; 0.13 per cent is the figure given by Marshall⁸ for lower segment cesarean section in cases of favorable omen. Possibly in contracted outlet with an otherwise adequate pelvis induction still has a place.

Before leaving the subject of disproportion, I should say that there was one maternal death following separation of a placental previa with severe antepartum hemorrhage, and the incidence of maternal morbidity was a little less than the over-all figure given earlier.

TABLE IX. METHODS OF INDUCTION AND FETAL LOSS IN DISPROPORTION

METHOD OF INDUCTION	NO. OF CASES	FETAL LOSS	
		NO.	PER CENT
Rupture of membranes	33	7	21.2
Low	8	1	12.3
High	14	4	28.8
Not stated	11	2	18.1
Stomach tube	115	14	12.2
Animal bladder	61	5	8.2
Bougie	6	2	33.3
Total	215	28	13

Pre-eclamptic Toxemia.—

Last, I want to turn to pre-eclamptic toxemia, and I have little to say. In 446 cases there were 5 maternal deaths, one from postpartum hemorrhage, 2 from pulmonary embolism, one from eclampsia, and one from infective endocarditis (*Ps. pyocyanea*). The last must be attributed to the induction and could have been avoided probably by doing a cesarean section early; also I think the death from eclampsia might well have been avoided if a cesarean section had been done as this was a severe case of toxemia, and the patient did not go into labor quickly after rupture of the membranes. Stillbirths and neonatal deaths numbered 65 (14.6 per cent), but of these only 14 could be attributed to the induction, an incidence of 3.1 per cent.

McIntosh Marshall in his paper on cesarean section already referred to, given to the Twelfth British Congress of Obstetrics and Gynaecology in 1949, gives figures for pre-eclamptic toxemia. The cases were taken from sixteen teaching hospitals, and altogether there were 560 operations with 9 maternal deaths (1.61 per cent, but only 0.8 per cent from the lower segment operation). Stillbirths and neonatal deaths were 103 (17.7 per cent). I am sure I can safely presume most of the cases were severe toxemias. From these figures it does not appear that there is much to choose between induction and cesarean section as regards the baby; the former, however, would appear to be rather safer for the mother. I consider it wise, all the same, to do a cesarean on any patient with severe pre-eclamptic toxemia if she does not quickly go into labor after induction; also I would often operate upon an elderly primigravida with toxemia without induction at all. Further, study of the induction-delivery intervals shows that before 34 weeks they are very long, with a correspondingly big risk of antepartum infection, so that there is, I believe, good reason for believing that cesarean section is the best way to deliver at this period of pregnancy if it must be undertaken so early.

Summary

Surgical induction of labor is not without risk to the mother, and should not be lightly undertaken. It has, I believe, an important place in the treatment of postmaturity, anyhow in primigravidas; it can reduce the fetal loss, also the incidence of difficult labor in this class of case. Induction has no place, I believe, in the treatment of disproportion in primigravidas, and almost no place in multiparas. In pre-eclamptic toxemia, induction has an established place, in the interests of both the mother and the baby, but under certain circumstances cesarean section should be undertaken.

Of all the risks in surgical induction of labor, prolapsed cord is the most worrying, and if the head is above the brim the incidence is high. These

days, most of us I think would undertake cesarean section if this accident happens, but even so it is not always possible to recognize the condition in time to save the child.

It will be interesting for me to learn how far the use of Pitocin drips has added, if at all, to the safety of surgical induction in the classes of case discussed. Although I have had relatively little experience with it, I would hesitate to use it in postmaturity or in pre-eclamptic toxemia on account of increasing the already present risk of anoxia in the child.

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Discussion

DR. DAVID N. BARROWS.—What role did the midwives play in these cases?

MR. BLAIKLEY.—Perhaps I ought to explain the setup of our department which applies I think to all the English teaching hospitals and to the Scotch, Irish, and Welsh as well. The midwives deliver hardly any patients. They act as maternity nurses. All the normal patients are delivered by the students supervised by qualified men of varying seniority. The difficult cases are dealt with by the intern supervised by the registrar, who is a man with six, seven, up to ten or eleven years' experience. In some of the difficult cases the consulting surgeons will come along and deal with the cases themselves. The private service is quite separate from the department itself. There has not been at Guy's Hospital—and this applies to all except one or two other hospitals—what you call a chief of service. My own position is that I have over-all control of teaching, but clinical control of only one-half of the service. Four members of the staff are in charge of beds and these men are free to act independently. For all that, there is an over-all fair cohesion and there is no wide difference in method and ideas.

During the period, the practice of induction in primigravidas disappeared long ago, in the early nineteen thirties. Induction in certain cases of disproportion in multiparas, where there has been a difficult forceps delivery with the first, has persisted to some extent.

DR. JUSTIN T. CALLAHAN.—I would like to have Mr. Blaikley's criteria for postmaturity.

MR. BLAIKLEY.—In my country it is usually pretty easy to be certain about the dates. These women all attend in the early weeks of pregnancy. Most of them will come up at two months to book and with rare exceptions be seen by three months. One can check on those dates by the size of the uterus in the early months of pregnancy when it is most reliable and I think one can be pretty sure that the great majority of these listed are actually postmature. I do not worry about these cases until they are 2 weeks postmature, for the real danger comes at 43 weeks. You have, of course, to allow for an irregular menstrual cycle, such as one with a 35 or 42 day interval.

DR. LOUIS M. HELLMAN.—The question of postmaturity has been of great interest to me because, as Dr. Callahan indicated, it seems very difficult in this country to determine which patients are postmature. Unfortunately, at least in Brooklyn, our ladies don't have quite as accurate calendars as they have in London, and I am very much afraid that with

some of our Negro population, if we induced labor at 41 or 42 weeks, or even 43 weeks, we might be in serious difficulty. This is the kind of problem we met in Baltimore when we have tried to apply some of Mr. Blaikley's criteria there. I am convinced, however, that there is such an entity as postmaturity and if we were able to determine which patients were postmature, we could diminish the infant death rate to a certain extent.

Induction of labor for pelvic contraction I think has some historic interest and if I remember correctly, the first patient, the first woman to be given an anesthesia in labor was such a patient, whose labor was induced prematurely with the contracted pelvis. I think that some of the other people here might talk to better advantage than I on the induction of labor for pre-eclampsia. I still am not convinced that a great many infants can be saved by earlier delivery in ordinary toxemia. I think the place where babies can be saved is in cases of hypertension with superimposed pre-eclampsia. It is in this group that we have the highest fetal loss and there may be a saving.

PRESIDENT McLANE.—Dr. Blaikley would like to have us tell him about Pitocin drip induction in pre-eclampsia or in postmaturity. We would induce labor in patients with pre-eclampsia with Pitocin if they were not improving under treatment. We would perform the induction, I think, after the thirty-sixth week. We may not be radical enough after the thirtieth week in this country and by cesarean sections in pre-eclampsia we might save some babies. The figures at the New York Hospital show that as the incidence of cesarean section increases in these patients with early pre-eclampsia, our fetal mortality decreases after it. After the thirty-sixth week there is not much of a problem, particularly in multiparas, and even in primiparas labor can be induced pretty easily with Pitocin.

Postmaturity—I am afraid we do not think about it as much as you do. We do see a lot of patients who by their dates are two and three weeks overdue. We do not induce labor routinely on that indication alone. We might use Pitocin to induce labor in multiparas if we thought they were postmature but we are not inclined to in primiparas.

DR. R. GORDON DOUGLAS.—I think possibly from some of the discussion, we have forgotten to some extent that your series of patients started back in the nineteen twenties. I am sure that your policies have changed as you have indicated. When you summate the results in a series of cases started back in the twenties up to 1952, there will be included in the light of our present practices some unfortunate experiences that we hope we will not have in the years to come.

With respect to induction with one of the substances of posterior lobe, we have had some experience with the commercial Pitocin which contains a varying amount of Pitressin, also with the purer substance, and more recently with the synthesized chemically pure substance. I think in the light of our experience as far as we have gone these substances all act essentially similarly.

There is one possible misunderstanding concerning the use of Pitocin and you mentioned the fact that you have to or may have to use a large quantity of solution. We answer that by the fact that there is a tremendous variation in the amount of this drug that is needed in individual patients. Hence in commencing an induction of labor it is essential that we start with the very smallest amount and it does not matter how much we have to add, we induce a physiological type of labor. It can be discontinued instantaneously and in our experience fetal distress has not been a serious complication in the induction, but we may use 30 times as much in one patient as we would use in another to induce a physiological type of labor.

THE USE OF CONTINUOUS EPIDURAL COMBINED WITH CONTINUOUS CAUDAL ANESTHESIA FOR LABOR AND DELIVERY

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THE use of combined continuous epidural anesthesia and continuous caudal anesthesia in obstetrics has been described by Cleland.¹ A series of cases has not yet been reported, however, where minimal quantities of agent were used in a continuous epidural and continuous caudal anesthesia throughout labor and delivery.

Graffagnino and Selyer² reported 76 cases in which as much as 50 c.c. of the anesthetizing agent was injected into the second lumbar epidural space for labor and delivery. This technique resulted in severe hypotension in 3 of their cases, and heroic measures were required to save the mother in 2 of these. The hypotension was probably brought about by the large amount of the anesthetizing agent used. Flowers and his associates³ recorded the use of smaller quantities of agent in epidural anesthesia, supplementing the epidural with other forms of anesthesia for labor and delivery. In neither of these series was continuous caudal used in combination with the continuous epidural as recommended by Cleland.¹ We have recently used the combination in 74 cases. It is the purpose of this paper to present our results with this method.

Technique

The patient was placed in a lateral decubitus position. A calibrated, radiopaque ureteral catheter, 3.5 mm. in diameter, was passed into the epidural space between the first and second lumbar vertebrae through a 16 gauge Tuohy needle. The hanging drop technique described by Gutierrez⁴ was used for the identification of the epidural space with the Tuohy needle. The catheter tip was then threaded upward so as to lie between the eleventh and twelfth thoracic vertebrae, and the needle carefully withdrawn over the catheter. A level at T₁₁ and T₁₂ was selected because, as Cleland⁵ demonstrated, the special visceral afferent sensory pathways of the uterus are components of the eleventh and twelfth thoracic nerves. These pain conductors ascend from the uterus with the sympathetic nerves of the aortic plexus. They pass without synapse through the sympathetic ganglia and the gray rami communicantes into the dorsal roots of the eleventh and twelfth thoracic nerves and thence up the posterior column to the brain. A block at T₁₁ and T₁₂ might reasonably be expected to relieve the pain of uterine contractions. It should not, and, in fact, does not, relieve the pain caused by pressure of the presenting part on the perineum, the impulses for which are transmitted through the pudendal nerves to the sacral plexus. The caudal anesthesia was used in combination with the epidural with this fact in mind.

With the patient still on her side, a similar catheter was introduced into the caudal canal through the sacral hiatus with a Tuohy needle, which was then carefully withdrawn over the catheter. A dressing was applied about both catheters and the patient placed on her back. A local anesthetic of 2 per cent Xylocaine* was used for the introduction of the catheters, and the process was invariably painless. For purposes of this study, the position of the catheters was checked by x-ray after delivery.

As soon as the obstetrician was sure that the patient was in true labor, 4 c.c. of 2 per cent Xylocaine was injected into the epidural catheter. Good labor was a prerequisite in all but 8 of our cases. In these 8 cases, uterine contractions were poor, and the epidural and caudal anesthesia was used in combination with intravenous Pitocin infusion.

As roughly 2 c.c. of agent will block one segment when introduced epidurally,⁶ 4 c.c. was expected to block both T₁₁ and T₁₂ when introduced between them. This proved to be so, as 4 c.c. of agent relieved the pain of uterine contraction in every case in which the catheter was properly placed. The 4 c.c. injection was repeated every one to two hours as needed.

Clinical Case Material

Injection into the caudal catheter was withheld until the presenting part had descended sufficiently to cause pressure or pain in the perineal area. This perineal pain was invariably not relieved by the epidural anesthetic, and was considered the signal for the injection of 8 c.c. of 2 per cent Xylocaine into the caudal catheter. Caudal injection was also repeated every one to two hours as required until delivery.

The material used in this study is outlined in Table I. The method described was used upon 52 primiparas and 22 multiparas. In the patients studied there was no selection as to weight, bony structure of sacrum, or parity. None of the cases presented contraindications to conduction anesthesia as noted by Lull and Hingson,⁷ such as bleeding, marked anemia, local infection, or diseases of the central nervous system. Two per cent Xylocaine was the drug used in all cases because of the previous good results of our anesthesia department with this drug despite occasional reports of central nervous system stimulation with it. No central nervous system stimulation was noted in any of our cases. The vertex presented in 71 of the 74 cases. There were 2 cases of breech presentation, and there was one brow presentation. We did not employ the method in cases of suspected cephalopelvic disproportion.

TABLE I. CLINICAL DATA ON PATIENTS TREATED

Primiparas	52
Multiparas	22
Vertex presentations	71
Breech presentations	2
Brow presentation	1
Toxemia	3
Elderly primipara	1

Results

The results of our experience are summarized in Table II. Complete relief from pain of labor and delivery was afforded in 52 of our 74 cases. The epidural anesthetic was ineffective in but 3 cases. These occurred early in our series, and in each the postpartum x-ray showed that the catheter had

*Astra Pharmaceutical Products, Inc.

been misplaced. Eight women initially experienced continued unilateral pain following epidural injection. These patients were instructed to remain supine to permit diffusion of the agent to the unaffected side, and relief of pain soon became complete.

TABLE II. EFFECTIVENESS OF ANESTHESIA

	NUMBER OF CASES	PER CENT
Satisfactory epidural and caudal	52	70.3
Failure of epidural	3	4.1
Failure of caudal	19	25.6
Total	74	

There were 19, or 25 per cent, failures of caudal anesthesia. Of these, 12 were due to anatomic difficulties in technique of insertion of the caudal needle, 4 to clogging of the catheters, and 3 to the catheter coming out of place during transfer of the patient from bed to stretcher or inadvertent pulling out of the catheter. This did not surprise us, as Black⁸ in his review of the anatomy of the sacrum states that 20 per cent of caudal anesthetics are doomed to failure because of such conditions as absent hiatus, partial or complete agenesis, bony septum, and angulation of the sacrum.

It was our clinical impression that the force of uterine contractions was affected by neither the epidural nor the caudal injections. There were no prolonged labors among the multiparas. A prolonged first stage of labor was recorded in 3 of the 52 primiparas. Intravenous Pitocin drip was used in all these 3 cases. The second stage of labor could be appreciably shortened by instructing the patient to bear down with each palpable uterine contraction, as the so-called "bearing down" pains were eliminated by the caudal.

The number of injections necessary varied with the duration of labor. The epidural injections, repeated every one to two hours, averaged 3 injections per case. The number of caudal injections used averaged only 1.5 per case. It is significant in evaluating the method that about half of the cases required only one caudal injection. The question is therefore raised as to whether there is enough benefit from the introduction of a caudal catheter to warrant its use in place of a single-shot caudal anesthetic or a malleable Hingson caudal needle without catheter.

There were no serious systemic reactions in our patients. In 3 cases there was a transient and slight fall in blood pressure. By confining our epidural injections to 4 c.c. at a time, and by using only 8 c.c. of agent in our caudal injections the problem of severe hypotension was eliminated. Hallet⁹ reported an incidence of 8 per cent hypotension necessitating therapy.

TABLE III. TYPES OF DELIVERY

	NUMBER OF CASES	PER CENT
Spontaneous	25	35.2
Low forceps	38	51.3
Low midforceps	8	10.8
Partial breech extractions	2	2.7

TABLE IV. SUMMARY OF COMPLICATIONS

Delayed breathing time	4
Intrapartum fetal death	1
Superficial infection in caudal area	2
Prolonged first stage of labor (over 24 hours)	3
Prolonged second stage of labor (2 hours or over)	11
Hypotension, mild, transient	3

The methods of delivery employed are summarized in Table III. Prophylactic low forceps were used in 51 per cent of the cases. Seventy-five per cent of the primiparas had low forceps deliveries. Forceps rotations were used in 6 cases and the vertex was rotated manually in 5 cases. There was one posterior brow presentation in our series. The brow was converted to a vertex by the Thorn maneuver and, after manual rotation to the anterior, delivery was accomplished with a low midforceps application. The excellent perineal relaxation afforded by the caudal anesthesia facilitated this operation.

In every case, the third stage of labor was rapid and uneventful. There were no postpartum hemorrhages or retained placentas. The third stage of labor in all these cases was treated with Ergotrate, 0.2 mg. intravenously, after delivery of the placenta.

In all except 4 cases the newborn infant breathed spontaneously without delay and the cry was lusty. In 3, resuscitation was accomplished without difficulty with suction and endotracheal intubation. We can offer no explanation for their failure to breathe spontaneously.

There was one unexplained intrapartum fetal death. This occurred in a patient who was a gravida iv, para iii. The fetal heartbeat was lost during the first stage of labor. There was no apparent obstetric reason for the tragedy, and autopsy failed to reveal a cause of death.

Summary

The method advocated by Cleland¹ for the use of continuous epidural and continuous caudal anesthesia for labor and delivery has been reviewed. The results of its use in 74 cases have been presented. Completely satisfactory anesthesia for labor and delivery was afforded 70 per cent of the patients. The results with the continuous epidural anesthesia were gratifying, there being only 3 failures and these due to incorrect placement of the catheter. The continuous caudal left something to be desired in view of its occasional technical difficulty. Furthermore, the necessity for the introduction of a caudal catheter remains open to question, as about half of our patients required only one caudal injection. No serious complications were encountered in our series except for one unexplained intrapartum fetal death. The results thus far justify the continued trial and evaluation of the method.

We are indebted to Dr. Donald Brace, Chairman of the Department of Anesthesia (recently deceased), and Dr. Clair E. Folsome, Chairman of the Department of Obstetrics and Gynecology, for their advice and encouragement in this work.

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PERINATAL MORTALITY ASSOCIATED WITH CESAREAN SECTION

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IN 1939 Schumann¹ estimated that the maternal mortality following the cesarean operation throughout the United States averaged 5.8 per cent while the infant loss approximated 8.5 per cent. With the more general acceptance and practice of improved obstetrical care, hospitalization for even the apparently normal delivery, availability of banked blood, experienced assistants and modern therapeutic measures, the death rate among expectant mothers has been greatly reduced.

At the same time, despite these improvements, the perinatal loss with deliveries by section continues to be shockingly high. As shown in Table I, the reported perinatal mortality rate varies from 3.7 to 13.5 per cent. Consequently, before acceptance of a cesarean section as a satisfactory treatment of the many problems and complications which have been thought to indicate its use, additional evaluation should be made concerning the risk to the fetus.

TABLE I. PERINATAL MORTALITY

HOSPITAL	NUMBER OF SECTIONS	FETAL MORTALITY (%)
Cincinnati General (1940-1949) ²	251	5.1
Boston Lying-in (1934-1943) ³	1,736	6.8
Johns Hopkins (1896-1941) ⁴	1,333	6.0
State of Mass. (1937-1941) ⁵	--	8.2
Chicago Lying-in (1942-1949) ⁶	--	5.9
City of New Orleans (1927-1936) ⁷	1,108	10.8
Sloane Hospital (1942-1947) ⁸	--	3.7
Loyola University (1938-1947) ⁹	--	7.8
Chicago Lying-in (1938-1942) ¹⁰	500	9.2
St. Vincent's, New York (1932-1946) ¹¹	--	9.7
New York Lying-In (1933-1949) ¹²	1,834	7.7
Methodist Hospital, Brooklyn (1936-1946) ¹³	768	4.9
Philadelphia Lying-In (1932-1942) ¹⁴	1,322	9.2
Pittsburgh (1940-1949) ¹⁵	118	13.5
New York Univ.-Bellevue Center (1942-1951) ¹⁶	654	8.8
Tulane University ¹⁷	1,219	5.6
Beth-El, Brooklyn (1945-1951) ¹⁸	969	4.5
Buffalo General and Children's (1944-1953)	944	6.3

Material

This study includes all deliveries in the maternity sections of two hospitals (Buffalo General Hospital and Children's Hospital) and all cesarean sections during the years 1944-1953, inclusive. This particular ten-year period was chosen for one reason: the availability and wider use of the antibiotic agents during that time.

Throughout this period both hospitals were operated by trained nursing personnel and resident staff, were equipped with an adequate blood bank, and

had available an excellent premature nursery. Each hospital accepts private patients who are managed by general practitioners as well as specialists, depending upon the individual's qualifications. All staff patients are treated by the resident staff under the guidance of the specialists. During the period surveyed, the same resident personnel served in the two institutions and virtually the same attending staffs practiced in both hospitals.

A total of 35,890 deliveries was reviewed. The perinatal loss was 1,052, an over-all perinatal mortality of 3.04 per cent. A total of 944 cesarean sections was performed in these institutions during this time, an incidence of 2.63 per cent. There were 951 babies delivered by 944 cesarean sections. The perinatal mortality in the sectioned cases was 6.3 per cent, with a corrected rate of 4.09 per cent.*

In an effort to determine the influence of the anesthesia and/or the type of operation on the perinatal loss, a group of "elective" cesarean sections was studied. The cesarean sections that were considered to be "elective" in nature were those which were not indicated by placenta previa, abruptio placentae, prolapsed cord, ruptured uterus, or an unsuccessful trial of labor. The latter was considered to be more than ten hours for primigravidas and more than six hours in multigravidas. In addition, those cases were excluded in which the maternal indication for section would be likely to influence the fetal outcome (severe toxemia, with the operation performed early for the mother's welfare, and diabetes). There were 677 patients in this group sectioned "electively," with a perinatal loss of 3.5 per cent, a corrected mortality rate of 1.9 per cent.

Fetal depression has been regarded as an important criterion of the effect of the anesthesia or the operation. The fetus was thought to be depressed when respirations failed to be initiated within one minute, or whenever some positive means of resuscitation (excluding aspiration) were required.

TABLE II. FETAL DEPRESSION AND MORTALITY ACCORDING TO ANESTHESIA AND OPERATION

ANESTHESIA AND TYPE OF OPERATION	NO. OF OPERATIONS	RESPIRATORY DEPRESSION (%)	DEATHS	
			NO.*	%
<i>Spinal Anesthesia.</i> —				
Flap operation	257	14.4	4	1.5
Classical and Porro sections	166	20.4	1	0.6
Total	423	16.7	5	1.18
<i>General Anesthesia.</i> —				
Flap operation	99	15.5	1	1.1
Classical and Porro sections	155	17.4	2	1.2
Total	254	16.5	3	1.14

*Excludes macerated stillborn infants, those with abnormalities incompatible with life and erythroblastosis, infants of diabetic mothers, and immature infants delivered of mothers with severe toxemia.

There were 281 classical procedures, 356 low segment (flap) procedures, and 40 cesarean hysterectomies. In determining the effect of the procedure on the fetus, the cesarean hysterectomy and the classical varieties were combined because of the usual similarity of the operation until the infant is delivered. There was a perinatal mortality of 1.4 per cent with the flap operation and 0.9 per cent with the classical operation; respirations were depressed in 14.5 per cent and 19.3 per cent, respectively.

*The corrected rate was determined by excluding all macerated stillborn infants, those with congenital abnormalities incompatible with life, and those who died in the neonatal period whose initial weight was less than 1,500 grams.

There were 423 patients delivered under a spinal anesthetic with an associated perinatal mortality of 1.18 per cent and a fetal depression rate of 16.7 per cent; 254 patients were delivered under a general anesthetic with an associated perinatal mortality of 1.14 per cent and a fetal depression rate of 16.5 per cent.

In the "elective" group, under spinal anesthesia, there was respiratory depression in 20.4 per cent with the classical procedure and in 14.4 per cent with the flap type of operation. The perinatal mortality was 0.6 and 1.5 per cent, respectively. Under general anesthesia the respirations were depressed in 17.4 per cent with the classical procedure and in 15.5 per cent with the flap procedure. The perinatal mortality was 1.2 and 1.1 per cent, respectively.

Perinatal Deaths in Relation to Indications for Sections

Since these factors seemed to have little apparent influence on the incidence of fetal depression, perinatal deaths have been also considered in the light of the indication for the section.

The highest rate of fetal loss was associated with a single case of vasa previa, in which a 5 pound, 10 ounce stillborn infant was delivered.

There were 6 patients previously sectioned who were sectioned again because of signs of a ruptured uterus, an incidence of 1.5 per cent rupture in previously sectioned patients. There were no maternal deaths associated with ruptured uteri, but 3 infants were lost, a perinatal mortality of 50 per cent.

Cesarean section was thought to be indicated by premature separation of the placenta in 33 cases, or 3.4 per cent of the patients operated upon. Thirteen infants were lost (39.3 per cent). Placenta previa was considered an indication for section in 42 cases, or 4.4 per cent of the patients operated upon. This included marginal and partial previa as well as central placenta previa. Of these, 15 were central placenta previa. A total of 10 infants was lost, a perinatal mortality rate of 23.8 per cent. One was a stillborn infant that weighed 4 pounds, while the remaining 9 were premature and varied in weight from 1 pound, 12 ounces, to 4 pounds, 12 ounces.

Soft-tissue dystocia was considered the indication for operation in 5 instances; one case ended with the stillbirth of a 9 pound, 14 ounce infant following twelve hours of hard labor with a breech presentation in a multiparous patient whose cervix had previously been repaired.

Sections were performed on 12 patients (1.3 per cent) because of a prolapsed cord with the loss of 2 infants (16.6 per cent). Seventeen patients (1.8 per cent) were delivered by section because of the history of one or more previous stillbirths, with the loss of 2 infants (12 per cent); one because of prematurity and the other because of erythroblastosis.

Toxemia was considered the indication for section in 28 cases (2.9 per cent). All but 2 of these patients were primigravidas. There were 3 infants lost, a mortality rate of 10.7 per cent. All 3 were immature infants that weighed less than 1 pound, 8 ounces, whose mothers had severe and uncontrolled pre-eclampsia.

Twenty-three (2.4 per cent) diabetic patients were delivered by the section procedure with 2 infants lost (8.7 per cent). There were 37 cases (3.9 per cent) in which inertia was regarded as the indication for cesarean section. None of this group had been in labor less than thirty hours. Three infants were lost (8.1 per cent) with a corrected mortality rate of 2.7 per cent.

In this series elderly primigravidas, considered to be those patients whose first pregnancy occurs after the age of 35 years, were frequently delivered by

cesarean section because of the improbability of many subsequent pregnancies. Of 66 such patients, 2 left the hospital without a live infant, an infant loss of 3.0 per cent with a corrected loss of 1.5 per cent.

In the entire group of 944 patients, a previous cesarean section was considered to be the indication for the cesarean operation in 385 cases, or 40.7 per cent. Of these, there were 10 infants lost, a mortality rate of 2.5 per cent, with a corrected rate of 1.8 per cent.

Some degree of disproportion was the indication for cesarean section in 250 patients (25.8 per cent of the group). This was substantiated in 144 cases by roentgen pelvimetry. In all probability some of these patients actually had dystocia due to malpresentation or inertia rather than to a true disproportion. Included in this group were 11 who had a malpresentation of the vertex (8 brow presentations and 3 face presentations) and 5 cases of failed forceps. An infant loss of 5 (2.0 per cent) was encountered, with a corrected perinatal mortality of 1.5 per cent.

TABLE III. PERINATAL MORTALITY ACCORDING TO SECTION INDICATION

INDICATION	NUMBER	INCIDENCE* (%)	PERINATAL DEATHS	PERINATAL MORTALITY (%)
Vasa previa	1	0.1	1	100.0
Ruptured uterus	6	0.6	3	50.0
Abruptio placentae	33	3.4	13	39.3
Placenta previa	42	4.4	10	23.8
Soft-tissue dystocia	5	0.5	1	20.0
Erythroblastosis	11	1.1	2	18.1
Prolapsed cord	12	1.3	2	16.6
Previous stillbirth	17	1.8	2	12.1
Toxemia, acute	28	2.9	3	10.7
Diabetes	23	2.4	2	8.7
Inertia	37	3.9	3	8.1
Elderly primipara	66	7.0	2	3.0
Previous cesarean section	385	40.7	10	2.5
Disproportion	250	25.5	5	2.0
Miscellaneous	89	9.4	2	2.2

*There was more than one indication in 6.4 per cent of the cases.

With 2 exceptions the remaining miscellaneous group, comprising 9.4 per cent of the total, were operated upon without a fetal loss. The considered indications were: transverse lie, 20, all but 2 of whom were in labor and had ruptured membranes or prolapsed small parts; fibroids, 13; previous surgery on the uterus, 10; cardiac conditions, 4; bowel obstruction, 3; tubal ligation, 2; congenital abnormalities in the mother, 2; and one each, compound presentation, carcinoma of the cervix, ulcerative colitis, hip fixation, broad ligament varicosities, previous cerebral hemorrhage, previous postpartum hemorrhage, acute appendicitis, tuberculosis, and an "incarcerated, sacculated" pregnancy. Of the 2 infants lost, one weighed 5 pounds, 10 ounces, and was stillborn, delivered of a mother in shock with a bowel obstruction, while the other was a 3 pound, 4 ounce stillborn infant in the "incarcerated" pregnancy.

Summary of Indications Associated With Perinatal Losses

To summarize, in the 677 patients who had elective cesarean sections (as defined above) there was a fetal loss of 3.5 per cent, with a corrected perinatal mortality rate of 1.9 per cent. In a group of 842 cesarean sections including all indications except emergency situations, i.e., omitting ruptured uteri, bleeding, bowel obstruction, and prolapsed cord, there were 30 infants lost (3.5 per cent), a corrected perinatal mortality rate of 2.1 per cent.

Of the 60 perinatal deaths which occurred in the total of 944 cesarean sections, 25 (41.6 per cent) were stillbirths (2.6 per cent of all sections). The stillbirths can be assigned to the following causes: asphyxia due to premature separation of the placenta, 9; antepartum asphyxia of unknown etiology, 5; asphyxia due to ruptured uterus, 3; asphyxia due to prolonged labor, 3; congenital anomalies of the fetus, 2; asphyxia due to placenta previa, 1; asphyxia due to vasa previa, 1; asphyxia due to maternal shock (bowel obstruction), 1.

The 35 neonatal deaths may be assigned as follows: prematurity and atelectasis, 16; prematurity with hyaline membrane disease or hyaline membrane disease itself, 8; congenital anomalies of the fetus, 4; erythroblastosis, 3; atelectasis, 2; pneumonia, 1; cerebral damage, 1.

Comment

At these institutions all babies weighing less than 2,500 grams at birth are considered to be premature and are managed accordingly. Approximately 8 per cent of all vaginal deliveries terminate in premature labor, with an overall perinatal mortality in all types of delivery of almost 19 per cent, and a mortality of 6.7 per cent in infants between 1,500 and 2,500 grams.¹⁹

In this group of 944 sections, there were 97 premature infants delivered by 91 cesarean sections. Of these 97 premature infants, 33 (or 34 per cent) were lost (including 10 stillbirths). These 33 deaths due to prematurity in approximately 10 per cent of the cesarean sections account for 55 per cent of the total perinatal loss in the entire series of 944 sections. Even in the elective cases, 55 premature infants (9.4 per cent) were delivered, only 14 of whose mothers had started in labor or had ruptured membranes. Thus we observe preventable premature birth in 7.2 per cent of elective sections—in which the time for delivery was selected by the operator. It should be emphasized that in cases in which the time for an elective section was arbitrarily selected (excluding severe pre-eclampsia, in which the maternal welfare outweighed the fetal survival) the perinatal loss was almost 10 per cent.

In the analysis of the cause of infant mortality in cesarean section the usual factors accounting for perinatal loss are encountered in addition to the complicating factors necessitating the procedure. Abnormalities incompatible with life are of course unavoidable. Evidence of faulty judgment in timing the procedure and in estimating the size and development of the infant are shown in the elective delivery of the occasionally markedly premature infant. Although the delivery of a known dead infant by cesarean section is usually unnecessary, occasionally it may be justifiable for the sake of the mother.

Statistical data regarding the incidence of perinatal death associated with cesarean section often fail to indicate the true risk of this type of delivery to the fetus. We believe this can best be accomplished by a review of the perinatal loss when sections are considered in groups according to the indication for the procedure.

The care of the newborn after cesarean section is without question an important adjunct in diminishing neonatal loss. In the institutions from which this review has been taken the routine has included minimal quantities of narcotic or no premedication, immediate suction of the nasal passages and gastric contents of the newborn, and immediate placement in a properly humidified, heated, and isolated nursery unit.

Summary

1. A report is presented of the perinatal mortality associated with cesarean section, with a review of 944 cesarean sections with respect to the factors accounting for the infant loss.

2. The perinatal mortality with cesarean section is approximately twice as high as the over-all perinatal loss in all types of delivery.

3. Neither the type of anesthesia nor the type of operation seemed to have any particular bearing on the ultimate outcome of the newborn.

4. Forty per cent of the perinatal loss can be attributed to asphyxia due to placenta praevia and placenta abruptio.

5. Almost 50 per cent of the perinatal loss can be attributed to emergency situations where there is little chance for fetal salvage.

6. The perinatal mortality in strictly elective cesarean sections is slightly higher than the over-all perinatal mortality.

7. There appears to be an inherent perinatal loss with cesarean section of approximately 1 per cent, in which death could be attributable only to "hyaline membrane disease" or atelectasis. However, of the 8 infants who died of these causes in the elective cesarean sections, 5 were premature.

8. In those cesarean sections indicated by fetopelvic disproportion the perinatal outcome appears to be somewhat better than the over-all loss in all types of vaginal delivery.

9. Approximately 10 per cent of the perinatal loss can be attributed directly to prematurity. In an additional 25 per cent, prematurity was a contributing cause leading to death.

Conclusions

1. The immediate care of the newborn is important but the best of care will not alleviate more than a small part of the high perinatal loss associated with cesarean sections.

2. A reduction in the perinatal mortality can be accomplished if every effort is made to avoid the delivery of the premature infant. The usual incidence of prematurity could be lowered by awaiting the onset of labor in the majority of elective sections and by a more conservative management of placenta previa.

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SUBTERM INDUCTION OF LABOR IN THE MANAGEMENT OF ERYTHROBLASTOSIS FETALIS

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THE treatment of erythroblastosis fetalis is a problem for both the obstetrician and the pediatrician. Gainey and associates⁷ state that "to date the obstetrician has contributed little constructive information" but "instead it is suggested that more has been done to aggravate the situation in many instances." Obstetricians have often failed to recognize important criteria that might point to the need for early delivery in the Rh-negative mother who has a history of previous difficulty or an antibody titer which should alert him.

Because we have lost several full-term babies as stillbirths and have delivered a few who have died immediately after birth with hydrops fetalis or failure to respond to full exchange transfusions, we have delivered deliberately a series of babies ten days or more before term. The statistical data concerning the patients at full term with past histories of severely erythroblastotic infants and those who have been delivered early are presented here. Prematurity should not be added to the problem of erythroblastosis if there is a possibility the fetus may survive if permitted to go to term. However, there is a period before term when greater salvage can be expected without increasing the dangers of kernicterus or death. Many authors entirely disregard the erythroblastotic babies who have died in this period before reaching term. Many of these can be salvaged, and should be considered as fatalities of the full-term concept.

Previous Reported Opinion

Many authors have stated that premature induction is not a worth-while procedure to employ in the management of erythroblastosis fetalis. Hughes¹¹ reports that "although it was formerly advocated that labor be induced early in order to avoid further damage to the fetus, incurring of the risks of prematurity is now judged to be more dangerous than permitting the pregnancy to go to term. It has been generally concluded that chance of survival is greater than for one who, in addition to hemolytic disease, has all the handicaps of prematurity." Vaughan, Allen, and Diamond¹⁸ add that "immaturity in a liveborn baby with erythroblastosis carries an increased risk of unfavorable outcome, particularly with respect to kernicterus," and they feel that the "induction of labor should be reserved for those instances in which the likelihood of stillbirth is great, such as in mothers with high titers who had previous infants stillborn because of erythroblastosis." The same authors⁸ in a later contribution state that "early induction of labor should be avoided rigidly."

Mollison and Walker¹⁴ found that "routine induction of labor three to five weeks before expected delivery in Rh negative women resulted in lower infant survival rate than when labor was allowed to proceed spontaneously." They also noted that "severely affected immature infants had a lower recovery incidence even on exchange transfusion therapy."

Other articles in the current literature, however, temper the stand against induction of labor. Abelson¹ writes, "Our group has assumed a conservative attitude towards early delivery of the Rh-sensitized woman." The hope is not routinely held out that induction of labor will influence the outcome favorably. But they "cannot believe that early delivery never should be permitted." In Mollison's series treatment was decided by a series of random numbers and the premature babies did not all receive exchange transfusion, nor was re-exchange transfusion used. The facts that (a) 30 per cent of the stillbirths may occur between the thirty-seventh and fortieth weeks, (b) the danger of kernicterus is not so great in this group as in the more immature babies, and (c) exchange transfusion will prevent kernicterus lead us to believe that if certain criteria are met, early delivery may be justified.

Gaffney⁶ feels "the question of early delivery of immunized mothers who are presumably carrying an Rh positive fetus is not yet completely settled. In general, early delivery is not to be advised" but it has been the practice of Gaffney to induce labor "in carefully selected cases, no earlier than 21 days before the expected date of delivery, and in these cases an exchange transfusion is started immediately after birth of the infant. The indications for induction of labor have been (a) the preceding pregnancy ending in hydrops; stillbirth or kernicterus; (b) a marked rise in antibody titer at the seventh or eighth month."

It should be emphasized that early induction is not a treatment in itself, but must be employed with prompt exchange transfusion.

In this presentation we wish to affirm the findings of Abelson,² Rolf,¹⁵ and others and encourage the obstetrician to take a positive role in the problem of erythroblastosis, thus aiding the pediatrician in decreasing the mortality of these cases. We propose induction in certain Rh problem cases between 10 and 28 days before term, that is, after the period when prematurity would in itself be a serious obstacle for the newborn.

Clinical Material

The material used for this study includes the last 4,000 patients from our private practice. The 4,000 patients represent 6,003 pregnancies. Study of the distribution of the Rh factor in these 4,000 patients revealed that 3,498 were Rh positive (87 per cent) and 502 were Rh negative (13 per cent). In 1,048 (17.4 per cent) of these 6,003 pregnancies, there was the possibility of erythroblastosis; that is, the mother was Rh negative and the father was Rh positive. Nine hundred and seventy-eight (93.3 per cent) of these showed no abnormal agglutinins in periodic titrations of their sera during the last trimester of pregnancy. Seventy (6.7 per cent) of these showed an antibody titer and were, therefore, potentially problem cases. The relative incidence of positive titrations in this group is reviewed in Table I.

TABLE I. FREQUENCY OF ABNORMAL AGGLUTINS IN RELATION TO PARITY

PARITY	POSITIVE TITERS		NEGATIVE TITERS	
	NO.	%	NO.	%
i	2	0.19	484	46
ii	17	1.6	289	27
iii	23	2.2	126	12
iv	17	1.6	60	5.7
v	8	0.77	16	1.5
vi	2	0.19	2	0.19
vii	1	0.09	1	0.09
Total	70	6.7	978	93.3

It is to this group of 70 pregnancies that we have directed our specific attention and discussion (Table II). Of these pregnancies, 37 (52.5 per cent) were those in which labor was induced before term or from two to four weeks prior to the expected date of confinement. Four cases in the induced-labor group cannot be considered, for 2 of these infants died of congenital defects, and 2 were hopeless cases, dying in utero before the thirty-sixth week. The exclusion of these leaves as possibly salvageable a group of 33 pregnancies.

In the group in which labor was not induced there were 33 cases. Of these, 14 must be excluded since 3 fetuses died of causes other than erythroblastosis and 11 died in utero before the thirty-sixth week. The remainder represented the 19 cases as possibly salvageable in the non-induction group. The reasons for not inducing labor in this group were (a) the titrations in the Rh-negative mother's serum were very low; (b) the baby was too small; (c) the cervix was not suitable for rupture of the membranes, or (d) there was no previous history of Rh incompatibility.

TABLE II. Rh PROBLEM CASES—TOTAL 70

	LABOR INDUCED		LABOR NOT INDUCED	
	NO.	%	NO.	%
Number of cases	37	52.5	33	47.5
Number of hopeless cases less than 8 months	4	10.8	14	42.4
Number of salvageable cases	33	89.2	19	57.5
Lived	29	87.8	9	47.3
Died	4	12.2	10	52.7
Weight 5 pounds or over	33	100	19	100
Pregnancy involved				
i			1	5
ii	6	18.1	9	49.4
iii	16	45.4	4	21
iv	8	24.4	2	10.5
v	2	6	1	5
vi	6	3	2	10.5
Titers in current pregnancy	30	90.9	17	84.4
1:16-1:256				
Titers in current pregnancy	1	0.03		0
1:1,056				
Titers in previous pregnancy	2	6.6	2	10.5
1:4				
Titers in previous pregnancy	21	63.6	6	31.5
1:16-1:256				
No titers in previous pregnancy	10	30.3	11	57.9
Stillbirths in previous pregnancy	2	6.6		0
Erythroblastosis in previous pregnancy	9	27.2	3	15.8
No. of cases 3 to 5 weeks early spontaneously, salvageable and transfused		0	2	10.5
No. transfused	28	84.8	9	47.3
Lived	24	85.7	5	55.5
Died of erythroblastosis	4	14.3	4	44.5
Died of other causes	2	7.2		

Clinical Results

Of the 33 pregnancies in the group with induced labor, 29 babies (87.8 per cent) lived and 4 (12.2 per cent) died. All of these babies weighed over 5 pounds.

Of the 19 pregnancies in the non-induction group, 9 babies (47.3 per cent) lived and 10 (52.7 per cent) died. All of these babies weighed over 5 pounds.

It is important to mention that 80 per cent of all the cases in both groups were second, third, and fourth pregnancies of the respective mothers.

These groups were also similar in that 30 (90.9 per cent) in the group with induced labor and 17 (84.4 per cent) in the non-induction group had titers in the current pregnancy between 1:16 and 1:256.

We feel that one of the significant points to emphasize in this series is that the cases in which labor was induced were actually more seriously affected cases and had a worse prognosis than those in the non-induction group. This is shown by the following statistics: (a) One patient in the induced-labor group had a current pregnancy titer of 1:1,056 and there were none in the non-induction group. (b) Two patients in the induced-labor group and 2 in the non-induction group had titers of 1:4 in the previous pregnancy. (c) There were 21 (63.6 per cent) in the induction group who had previous pregnancy titers between 1:16 and 1:256 and only 6 (31.5 per cent) in the non-induction group. (d) There was a history of stillbirths due to erythroblastosis in previous pregnancies in 2 cases in the induction group while in the non-induction group there were none. (e) Nine (27.2 per cent) of the patients in whom labor was induced had a history of erythroblastotic infants in previous pregnancies and only 3 (15.8 per cent) had such a history in the non-induction group. (f) There were 10 (30.3 per cent) patients in the induction group and 11 (57.9 per cent) in the non-induction group who had no history of increased titers in previous pregnancies, either because that pregnancy was their first one or because there had been no titers taken by the previous physician. It is interesting to mention that 2 patients in the non-induction group were delivered before term because of premature separation of the placenta. Both of these had been scheduled for induction. These 2 patients had poor previous Rh histories, had titers between 1:16 and 1:256, had had previous erythroblastotic infants, and delivered erythroblastotic infants, both of which required exsanguination transfusion. One of these patients delivered 5 weeks early and the other 3½ weeks before term.

There were 28 (84.8 per cent) infants transfused in the induction group and 9 (47.3 per cent) in the non-induction group. In the induction group 24 (85.7 per cent) lived and 4 (14.3 per cent) died. Two, or half of the infants that died, died of other causes than erythroblastosis, which leaves a corrected infant mortality rate in the induced-labor exsanguination-transfusion group of 2, or 7.2 per cent. In the non-induction group 4 (44.5 per cent) died.

It is important to point out in respect to the noninduction exchange-transfusion group that not only was the infant mortality rate high but that only 47.3 per cent survived to term. It seems to us, therefore, that it is within the last month of gestation that one has the opportunity to improve the salvage rate of the erythroblastotic infant.

Principles of Treatment

We realized early that there was a need for planned cooperation in the total care of the sensitized Rh-negative mother if the mortality and morbidity rates were to be reduced. The combined efforts of the obstetrician, pediatrician, and laboratory technician have been employed in the handling of our cases.

Indications for Induction.—

In this series, an attempt has been made to induce labor in the problem cases sometime during the month prior to the expected date of confinement. No specific time has been determined for this induction. General principles of good obstetrical care were observed throughout pregnancy. Each individual case has been evaluated clinically. (1) A careful history of previous preg-

nancies, miscarriages, and transfusions was obtained. (2) An Rh determination was done on each partner and when possible it was determined whether each partner was homozygous or heterozygous. (3) Titrations of the Rh antibodies were done monthly or bimonthly beginning at the sixth month of gestation and the results were carefully analyzed. The concentration of the titer is not an exact indication as to the final outcome or the specific prognosis of the newborn. We have noted, however, that rising or very high titers and decreased fetal activity are frequently indicative of a significant pathological condition in the fetus. (4) The increased or decreased activity was carefully analyzed in each case. Decreased fetal activity may also be indicative of significant pathological abnormality in the fetus. (5) The size of the fetus was judged clinically by external abdominal examination and, if indicated, by x-ray of the fetus. In this series all of the babies weighed 5 pounds or over. Early induction was performed only if there was evidence of severe sensitization; otherwise the baby was delivered at term and the pediatrician was called.

Method of Induction.—

Each of these patients was admitted to the hospital for early induction. Interruption of pregnancy was started in the delivery room under strict aseptic conditions. A sterile vaginal examination was done. The gloved finger was introduced through the cervical canal very gently, and the membranes were stripped from the lower segment of the uterus, following which the membranes were ruptured. The patient was then returned to her room where she remained in bed until labor began. No further inducement was required in the majority of cases, and labor began within a period of six to twenty-four hours. In those few cases where an added stimulus was needed, however, a course of quinine (2 grains every half hour for 5 doses) was given orally. If this medication was unsuccessful, intravenous Pitocin, 1 c.c. in 1,000 c.c. of 5 per cent glucose in water, was administered by the drip method. There were no failures of induction and there were no complications from the methods used. Labor began in all cases within twenty-four hours following rupture of the membranes.

Care of the Newborn.—

The accepted methods of the immediate care of the newborn were performed. The umbilical cord was left long and kept moist with warm saline packs. Specimens of the cord (fetal) blood were obtained and immediate laboratory studies were done on this blood. A complete blood count, Rh typing, Coombs test, total serum bilirubin, cross-matching, and study of the smear for nucleated red blood cells and platelets are the important procedures that should be followed.

Indications for Exchange Transfusion.—

In the event that the criteria of slightly to greatly depressed red blood cell and hemoglobin levels, elevated serum bilirubin, positive Coombs test, and decreased platelet count in an Rh-positive baby were obtained, particularly if other clinical evidence such as hepato- or splenomegaly were present in the baby, an exchange transfusion should be done without hesitation. This was done most conveniently through the umbilical vein route, although alternative techniques have been used successfully by other workers. Nothing was to be gained by vacillating if the above criteria were present, particularly in infants born more than 10 days before term.

There has been an increasing agreement regarding the management of the newborn infant with erythroblastosis fetalis (Vaughan, Allen,^{18, 19, 20} Gaffney⁶ and others). One or more exchange transfusions have been preferred to multiple small transfusions. Increased proficiency in the performance of the exchange transfusion has led to more definite indications and earlier treatment than prevailed previously when this technique was reserved for the late stages of erythroblastosis fetalis in the critically ill baby.

Procedure in Exchange Transfusions.—

In the instance of the subterm babies in our series, fresh type O, Rh-negative blood is available at birth. The infant's gastric contents are aspirated immediately after birth with a small rubber catheter, and the baby is kept warm and placed in oxygen. A catheter is placed in the umbilical vein as soon as the diagnosis of erythroblastosis fetalis is verified and the infant is given prompt treatment by exchange transfusion.

Our transfusion team consists of the pediatrician and two assistants, one of whom determines the status of the baby at all times and is prepared to control emergencies. Calcium gluconate is administered at each 100 c.c. exchange during the transfusion. If the baby's hematological status is alarming, we have found that a polyethylene catheter can be left tied in the umbilical vein to facilitate subsequent re-transfusions. The catheter is removed at the start of the second transfusion and a sterile one easily passed into the open track. The saphenous vein at the femoral junction may be chosen as the site of a second or third transfusion if they be needed and the umbilical route is not available. We have found, however, that it is frequently easy to insert the catheter into the dried umbilical stump after several days of life.

It is important to emphasize the need for fresh blood. The electrolyte disturbances are considerable under optimal conditions, and the use of old, stored blood is hazardous. The electrocardiogram has aided us in detecting hyperkalemia in several instances, and ideally should be available to the transfusionist.

After the exchange transfusion, adequate chemotherapy and careful nursery care comparable to that afforded a premature infant are necessary.

Results of Early Induction and Exchange Transfusion of the Newborn

Careful follow-up data on each baby of the series have given the pediatrician sufficient material to allow prognostic statements about survival and the presence of complications, particularly kernicterus. Failure to institute early therapy may result in death within the first days of life, or the development of kernicterus. These two complications have attracted most of the attention in our series of cases, and although the number managed is too small to permit precise recommendations, the conclusions seem striking, and call for similar, larger series to be studied elsewhere.

The gains that may be made in fetal salvage were in the most severely affected group. In this group, the history disclosed a previous pregnancy with a fetus macerated due to erythroblastosis or a live baby seriously affected. If the father is homozygous the future pregnancies have almost invariably been terminated in a stillbirth or a hopelessly erythroblastotic baby. The customary procedures at this point most often end in failure, and serve as mere gestures. The prospect of death in utero or on the day of birth may be expected from the history and clinical course of comparable cases. An occasional poor evaluation of size and miscalculation of date of confinement may add prematurity to the problem. This was a calculated risk, however, in an occasional case, in the light of almost universal success with this method of evaluating the subterm period.

Case Histories

The following case histories are prime examples of the policy we have adopted in problem cases:

CASE 1.—Baby S. was the product of the seventh pregnancy of an Rh-negative mother and a homozygous Rh-positive father. The past history of this couple was filled with erythroblastotic difficulties. There were four other living children. The two youngest were treated by their doctor with multiple small transfusions and survived without apparent

sequelae although each was markedly icteric. One miscarriage occurred at three months' gestation early in marriage and the sixth pregnancy resulted in a stillbirth at about 8½ months' gestation. The fetal activity had been noted to dwindle and finally cease completely.

With the patient's seventh pregnancy, the titer rose from 1:64 to 1:1,056 in the last month. The baby was due on or about July 26, 1953. The decision to induce labor was reached in view of the bad past history and because of marked change in the baby's activity. On June 29, 1953, a small child was delivered after obstetrical induction. The baby appeared listless, his color was poor, and there was marked pallor. His weight was 5 pounds, 9 ounces. He was type O, Rh positive. The Coombs test was positive. The red blood count was 1.72 million and the hemoglobin 7.0 Gm. The platelets decreased. The nucleated red count was 43 per 100 white blood cells. The liver was 3½ fingerbreadths below the right costal margin; the spleen 2½ fingerbreadths below the left costal margin. The total serum bilirubin was 9.4 mg. per cent.

An exchange transfusion was performed immediately after birth, and 295 c.c. of compatible Rh-negative blood given through the umbilical route, and 285 c.c. removed. Transfusion had to be halted due to the baby's poor general condition. The catheter was tied in place, and the baby was placed in an incubator and was given supportive treatment. Another replacement transfusion was done on June 30. After a stormy course the baby was discharged from the hospital on July 14 on the sixteenth day of life. He was in apparent good health, but the prognosis for ultimate normality was deferred. It is hard to visualize that intra-uterine death would not have occurred if he had been permitted to go to term. Development has been normal to date.

On June 19, 1954, Mrs. S. was delivered spontaneously of a hydropic stillborn infant. The estimated date of confinement was Aug. 15, 1954.

CASE 2.—Baby Paul T. was born April 1, 1952. This baby's mother presented a known hazard prenatally. Her first child was normal. The second was treated by his doctor with five small transfusions. The baby survived but was severely jaundiced and is spastic with speech and hearing retardation. During her third pregnancy (the present case) the agglutinin titer rose to 1:128, fetal activity slackened, and in the thirty-eighth week of pregnancy labor was induced. The amniotic fluid was icteric, and the baby was found to be cyanotic with a markedly enlarged liver and spleen and numerous purpuric spots. The blood count showed the hemoglobin to be 12 Gm., the red blood count 2.9 million. The platelets were reduced on the smear. The nucleated red count was 140 per 100 white blood cells. The Coombs test was positive. The baby's weight at birth was 6 pounds, 2 ounces. An exchange transfusion was done at 1½ hours of life. The baby developed moderate jaundice and the blood count was depressed for the first several weeks. Growth and development have been completely normal.

Summary

An analysis has been made of 4,000 private patients with 6,003 pregnancies, with special reference to cases of Rh incompatibility, their incidence and their treatment.

We feel that we are justified in stating that the obstetrician can and should assist constructively in the reduction of the mortality rate in erythroblastosis of the newborn.

Too many erythroblastotic infants die in utero during the last month of gestation; therefore, this month is crucial to the life of the infant. In selected cases as determined by specific criteria, subterm induction offers increased fetal salvage.

Induction should not be treated lightly but must be done only after careful and extensive clinical evaluation of each case. No specific time has been determined arbitrarily for this induction. In the hands of a trained team of

an obstetrician, pediatrician, and laboratory workers, this method can be employed successfully, usually without damage to the mother or the infant.

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THE SEVERITY OF DIABETES IN PREGNANCY

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THE increasing number of diabetic patients appearing in obstetrical clinics has stimulated a growing interest in the subject of diabetes in pregnancy. It is generally agreed that the incidence of complications and the fetal salvage bear a direct relationship to the severity of the diabetes; but unhappily there is no general agreement on what constitutes "severity" and how it is to be classified. There are two diametrically opposed schools of thought: (1) that severity should be based on longevity of the disease and on progression of vascular damage; (2) that the clinical status of the patient, in terms of the insulin requirement, is the best yardstick of severity.

White and her co-workers^{1, 2, 3} advocate what might be called the historical classification. Severity is graded on the basis of age at onset and duration of the diabetes, and on such objective findings as retinitis, vascular sclerosis, and renal damage. They pay no attention to insulin requirements. Pedowitz,⁴ on the basis of an experience with 156 viable pregnancies, concurs in this concept. The White classification, which has received virtually semiofficial recognition from this JOURNAL,⁵ is as follows:

Class A.—"Glucose tolerance test diabetes" or "chemical diabetes," requiring no insulin.

Class B.—Onset over age 20; duration less than 10 years; no vascular disease.

Class C.—Onset age 10-19; duration 10-19 years; minimal vascular damage.

Class D.—Onset under age 10; duration over 20 years; hypertension, retinitis, or minimal vascular sclerosis.

Class E.—Calcified pelvic vessels.

Class F.—Nephritis.

Occupying a neutral position on the subject, Oakley⁶ found no correlation between either age at onset or duration of disease, in a series of 267 English cases. Similarly Hurwitz,⁷ with 124 cases, reports a lower fetal loss in mothers requiring no insulin or in those whose diabetes was unmasked during the pregnancy, as compared with that in patients requiring insulin or those whose disease antedated the gestation. He concludes, "however, beyond this there appears to be no statistical difference in fetal mortality between patients with mild and those with severe diabetes, or between those with cases of short and those of long duration."

The leading advocates of the opposite point of view are Tolstoi, Given, and Douglas,^{8, 9} who consider the metabolic status of the patient, as expressed by the insulin requirement, to be the paramount criterion of severity. They believe that the woman, even without long duration or vascular damage, who

is prone to ketosis and who requires large amounts of insulin to remain in control, has severe diabetes. They feel that those who are "influenced by the degree and extent of vascular disease . . . have been measuring the concomitants or sequelae of diabetes and not severity as judged by difficulty in management."

In general we have leaned to this latter viewpoint. In 1953 we¹⁰ published the twenty-five-year experience with diabetes at the Providence Lying-In Hospital. In classifying the severity of our cases, we tended to follow the diagnosis of the internists concerned. This was usually predicated on the insulin requirement, with due consideration given to such factors as vascular and renal changes, and the "brittleness" of the diabetes. When we attempted to break down our cases into the White system of classification, we found that a substantial proportion of what we considered to be severe diabetics fell into White's relatively mild Class C. These patients exhibited a disproportionately high incidence of complications and fetal loss. Conversely, many of the cases which, because of essential hypertension, fell into the more severe White Class D, were clinically so mild as to require little or no insulin; and these contributed a minimum of complications and fetal loss. In our experience the White system of grading severity on a historical and vascular-damage basis alone is not entirely satisfactory.¹¹

All this confusion of evidence has intrigued us into a study of the problem. In order to be consistent, White's standard of viability (960 grams), her historical-vascular classification of severity, and the Joslin Clinic level of insulin "severity" will be used. The objectives are to attempt to evaluate: (a) what, if any, correlation there may be between the clinical severity, expressed in insulin requirement, and the physiological-obstetrical complications of pregnancy; (b) the relative importance of the insulin demand, as compared to the historical progression of the disease, in the determination of the severity of the diabetes.

Material

The material here presented comprises 204 viable pregnancies delivered at the Providence Lying-In Hospital in the twenty-eight-year period 1927-1954 (Table I.)

TABLE I. DIABETES IN PREGNANCY, 1927-1954

Total deliveries in the hospital		121,927
Total pregnancies in diabetic patients		219
Cases not included in statistics:		
Delivered elsewhere, etc.	3	
Nonviable (under 960 grams)	12	
	15	15
Cases used for this study:		
Hormone treated	21	
Non-hormone treated	183	
	204	204

Of these 204 patients, 21 received hormone therapy and 183 did not. Table II demonstrates that the results, with the exception of the section rate, are so comparable that both groups may be pooled as a single series for the

TABLE II. OBSTETRICAL COMPLICATIONS, HORMONE VS. NON-HORMONE THERAPY

	HYDRAMNIOS		PRE-ECLAMPSIA*		ACIDOSIS		CESAREAN SECTION		FETAL LOSS†	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Non-hormone (183 cases)	19	10.4	61	33.3	48	26.2	38	20.8	51	27.9
Hormone Therapy (21 cases)	8	38.1	6	28.6‡	6	28.6	16	76.2	6	28.6
Total series (204 cases)	27	13.2	67	32.8	54	26.5	54	26.5	57	28.0

*Applies to pre-eclampsia and superimposed pre-eclampsia in all charts and tables. Does not include 17 cases of uncomplicated essential hypertension.

†Fetal loss in all charts and tables refers to uncorrected gross stillbirth and neonatal loss of infants weighing over 960 grams.

‡This does not prove that stilbestrol prevents toxemia. Each case in the small group has a value of 5 per cent; one more patient would bring the figure above that of the non-hormone series.

purpose of this study. We are not now debating the merits of hormone versus non-hormone management, nor the question of cesarean section in diabetes. Our only comment on this chart is that we are not convinced that the results justify increasing the section rate to 76 per cent in the hormone group. Granting that two-thirds of these cases were severe diabetes by any standard, review of the records suggests that (in our personal opinion) a rate of about 48 per cent would have been appropriate in this particular group of women.

Distribution by White's Classification of Severity.

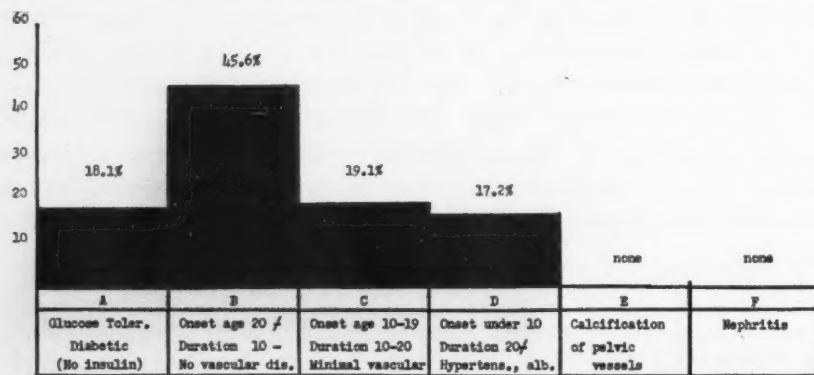


Fig. 1.

The series is distributed according to the White classification of severity in Fig. 1. It will be seen that two-thirds fall into the mild Classes A and B, while only one-third are in the more severe categories C and D. Although we had several patients suspected of renal damage, none of them could definitely be placed in Classes E or F. Of the women who had pelvic x-rays, none showed calcification of vessels.

This large number of relatively mild cases is attributable to two influences: (1) It is the type of spread commonly reported by obstetrical services, as distinguished from diabetic clinics. (2) The series goes back into the era when very few young diabetic patients or those with severe cases survived into the childbearing age. Until ten years ago the usual patient was the older woman with a rather mild case who was also frequently a multipara. It is only in recent years that we have begun to harvest the crop of primiparous, severely affected, juvenile diabetic patients.

Insulin Requirement

It has been our clinical impression that, although a few comparatively mild cases of diabetes seem to become "brittle" under the stress of pregnancy, most of the patients who give serious difficulty in control are those whose normal nonpregnancy insulin requirement is high. This aroused our interest in the comparative behavior of women with low and with high insulin demands.

The Joslin Clinic² classifies medical diabetes as follows, depending somewhat on the carbohydrate intake:

Mild.—Sugar free on 150 Gm. carbohydrate, without insulin.

Moderately Severe.—Sugar free on 150 Gm. carbohydrate and 10 units insulin; or more carbohydrate and 20-50 units of insulin.

Severe.—Requires over 50 units of insulin on 150 Gm. carbohydrate.

Since the pregnant woman usually consumes 150 Gm. or more of carbohydrate, 50 units is an appropriate standard of severity for this study. In the actual practice of our own clinic, the internists frequently label a case as severe at the 40 unit level of demand; and Given and associates⁸ mention that half their patients required 40 to 60 units a day, possibly implying that they regard 40 units as approaching the severe clinical range. If the data which follow were computed on the basis of 40 units as the critical level of severity, the curves shown would be more striking.

In order to be objective, however, this study is based on the 50 unit medically severe standard used by White's clinic. Furthermore, this is the *normal nonpregnancy requirement*, or that at the outset of gestation; *not the peak increase attained during pregnancy*.

Oakley⁹ states that "there is no significant difference between the fetal mortality in non-insulin-treated and insulin-treated diabetic mothers"; and Given and co-workers⁸ report a fetal loss of 22.6 per cent in patients not requiring insulin, as compared to 25.6 per cent in the women who used insulin. At first glance our results would appear to substantiate this, as the gross fetal loss was 28.2 per cent in insulin cases, and 27.3 per cent in nontreated women. The latter figure, however, includes 8 fetal deaths in patients who were acidotic when the disease was first discovered, or in acidosis due to gross negligence on the part of themselves or their physicians. If these preventable losses are corrected for, the fetal mortality in the women who *did not need insulin* was 14.9 per cent, or half that of the insulin-treated cases.

TABLE III. CHANGES IN INSULIN REQUIREMENT

	NO. OF INSULIN-TREATED CASES	PER CENT ALL INSULIN CASES	FETAL LOSS	REQUIREMENT OF 45 "INSULIN SEVERE" DIABETIC PATIENTS
Increased requirement	98	64.5	29.4%	38/45—84.5%
No significant change	40	26.3	27.5%	6/45—13.3%
Diminished requirement	14	9.2	21.4%	1/45—2.2%
Total	152	100.0	28.3%	

Note.—(1) The fetal loss increases slightly as the insulin demand increases.

(2) The "insulin-severe" diabetic patients exhibited an increased insulin requirement out of proportion to that of the insulin patients as a group.

It is recognized that the insulin requirement of some women increases, while that of others diminishes during pregnancy; but the statistics concerning these shifts vary widely in different reports. Our experience is recorded in Table III. Of the 152 patients who were on, or had recently been on, insulin at the outset of pregnancy: 64.5 per cent required more insulin; 26.3 per cent

showed insignificant fluctuations in either direction; and 9.2 per cent showed a definitely diminished requirement. Study of this table brings out two interesting points: (1) Although the figures are not very striking, the fetal loss follows the trend of the insulin demand, going up somewhat as the requirement increases. (2) The shift in requirement in the insulin-severe cases was out of proportion, as compared to the diabetic patients as a group. Of the 45 women with an initial level of 50 units or more, 84.5 per cent increased their demands; and only one (2.2 per cent) had a diminished demand. These are two of the fragments of information which lead us to consider the normal insulin requirement of the patient to be a matter of importance in evaluating diabetes in pregnancy, and cause us to regard the insulin-severe case with a jaundiced eye.

Acidosis

Interest in the insulin level naturally revolves around the problem of keeping the case in control. This is particularly vital in pregnancy. Several writers have emphasized the harmful effect on the fetus of even mild degrees of ketosis; and frank acidosis in our experience is by far the greatest single contributor to fetal death. It is, however, not very informative simply to tabulate the episodes of acidosis in pregnancy. It is important to understand some of the causes for break in control, and in what kind of women they occur. Table IV demonstrates that 61 per cent of the acidosis we encountered should have been preventable, and that this was associated with over one-third of the gross fetal loss in the series. By grades of severity, 60 per cent of the acidosis in Class B, 37 per cent in Class C, and 36 per cent in Class D was preventable; and, furthermore, 73 per cent of this preventable acidosis occurred in the "insulin-mild" patients. In other words, most of the trouble was with the women who should do the best; and it was too often the result of carelessness on the part of patient or physician.

TABLE IV. ACIDOSIS,* CAUSES AND FETAL LOSS

CAUSE OF BREAK IN CONTROL	CASES	PER CENT ALL ACIDOSIS	FETAL LOSS	
			NO.	%
1. Uncooperative patient	17	31.5	11	64.7
2. Inadequate medical supervision	11	20.4	8	72.7
3. Undiagnosed until in acidosis	5	9.3	3	60.0
4. Intercurrent infection	13	24.0	4	30.8
5. "Brittle" diabetes under competent medical management	8	14.8	3	37.5
Total acidosis	54	100.0	29	53.7

*The preventable acidosis in categories 1, 2, and 3 represents 61.2 per cent of all acidosis, and is associated with 38.6 per cent of the gross fetal loss in diabetes.

When this preventable element in the acidosis picture is corrected for, what might be expected is found: There is substantially more acidosis due to such factors as "brittle" diabetes and intercurrent infection in the patients whose insulin requirement is 50 or more units a day.

Obstetrical Complications

In addition to acidosis, two other physiological complications peculiar to pregnancy are evidently detrimental to the welfare of the fetus: pre-eclampsia, alone or superimposed on essential hypertension, and hydramnios. Singly or in combination, these three contribute to the great majority of perinatal fetal deaths.

Fig. 2 graphs these components, for insulin-mild and insulin-severe cases, in each of the White classes of severity:

Toxemia.—No correlation would be expected between insulin demand and the appearance of pre-eclampsia, and none exists. Half of the sharp rise in the insulin-severe cases in Class D is due to pre-eclampsia superimposed on the hypertension characteristic of that class.

Hydramnios.—This condition is a frequent concomitant of both toxemia and acidosis, and the incidence is consistently higher in insulin-severe diabetes.

Acidosis.—As previously mentioned, when preventable cases are corrected out, acidosis is more frequent in the insulin-severe case. Except in Class C, where both the gross and the corrected incidence is higher in the mild category. This may in part be accounted for by the fact that Class C contains the bulk of the unpredictable ten-year juvenile diabetic patients.

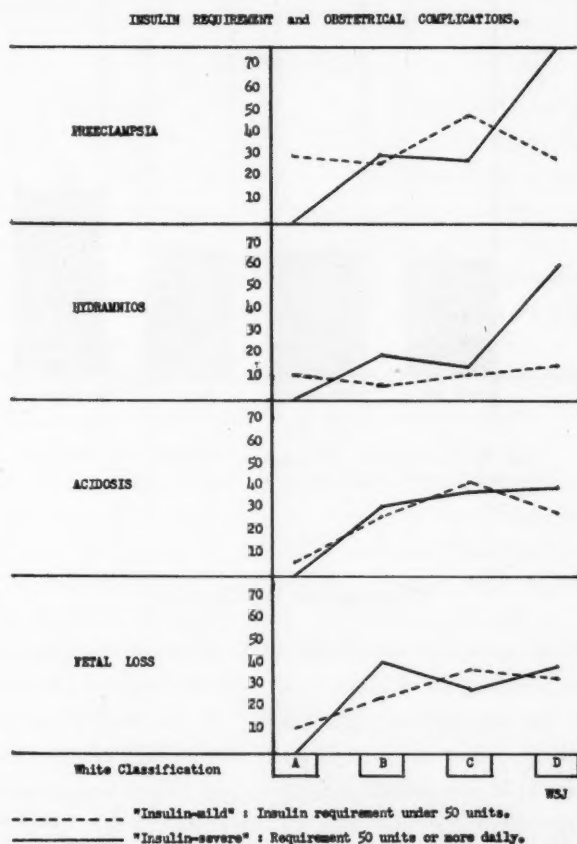


Fig. 2.

Another interesting finding is that there is less acidosis in the insulin-mild cases of Class D than among similar mild cases in Class C. Almost 60 per cent of these Class D women, despite their essential hypertension, had cases clinically so mild as to require from no insulin to less than 20 units. Although assigned a high severity rating because of their vascular disease, this group are not likely candidates for acidosis. In these relatively mild cases in older women the hypertension is the result of the normal aging process, and has little or nothing to do with either the duration or the severity of the diabetes.

Thus the hypertension in these cases serves only as a red herring, to confuse the results in the severity classification. This is certainly one of the defects of the White system.

Fetal Loss.—The gross fetal loss is higher in insulin-severe diabetes; except in Class C, where the peaks of pre-eclampsia and uncorrected acidosis coincide to produce a greater fetal wastage in the mild category.

Fig. 3 summarizes the findings: While the insulin-severe cases comprise only one-fifth of the diabetic series, they contribute more than their proportionate share of complications and of the resultant fetal loss.

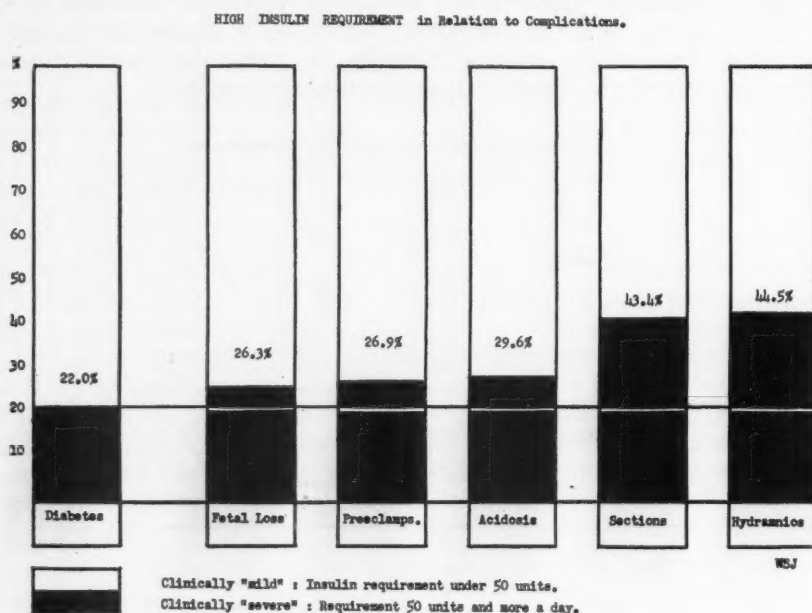


Fig. 3.

Evaluation of Results

In an attempt to evaluate these data, it must be remembered that although this is a sizable collection, as diabetes reports go today, the volume of material is actually small for statistical purposes. It provides an impression rather than proves anything concrete. In Fig. 2, the uphill climb of the curves across the field from A to D is reasonably consistent. This tends to uphold the validity of the historical-vascular concept of classification. Less consistent are the differences in level of the insulin-mild and the insulin-severe curves in Fig. 2; and less significant is the relative space occupied by "severe" in the more important blocks (acidosis and fetal loss) in Fig. 3.

From this one may surmise that: (A) There is a correlation between clinical severity, expressed in insulin demand, and the complications and fetal loss in pregnancy. (B) Insulin demand, however, appears to be less important than the historical and vascular progression of the disease in determining the severity of the diabetes.

Classification

The White classification has been a major contribution to the thinking in the field of obstetrical diabetes. It is basically sound; but in its present form it is too cumbersome, and certain technical difficulties in its application have been pointed out above. When employed in a study such as this it presents an immediate stumbling block: only a very large series is susceptible to being divided six ways, without ruining the statistical validity of the smaller components. If it is further subdivided (insulin mild and severe) into twelfths, confusion is compounded.

It should be possible to arrive at a more compact and workable classification. This might conveniently consist of four major historical-vascular classes of the White type, which could then be subdivided into insulin-mild and insulin-severe, for a total of not more than eight groups.

Conclusions

Two hundred four viable pregnancies in diabetic women are reviewed in an effort to ascertain what, if any, correlation may exist between: (a) the historical and vascular encroachments of the disease process; (b) the clinical severity as expressed by insulin requirement; and (c) the obstetrical complications and fetal loss. The information obtained suggests that:

1. The concept that age of onset, duration, and evidence of vascular damage are criteria of severity in diabetes is a sound one. It should probably remain basic in any classification.
2. There is also a significantly higher incidence of the physiological complications peculiar to pregnancy, and of fetal loss, in those patients whose normal daily insulin requirement is high (50 units and more).
3. Both these factors should be taken into consideration in the evaluation of the severity of a case of diabetes in pregnancy; and both should be included in the formulation of a definitive classification of diabetes in pregnancy.
4. The White classification is a good prototype, but there are certain practical objections to it in its present form. What is needed is a more simple and compact classification, embodying the principles here outlined.

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PREGNANCY COMPLICATED BY HYPERLIPEMIA*

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NORMAL pregnancy is associated with an increase in the concentration of lipids in the blood.^{1, 2} Boyd³ found that the plasma of nonpregnant young women contained an average of 181 mg. per cent of total cholesterol, 195 mg. per cent of phospholipid, and 154 mg. per cent of neutral fat. Corresponding values for women at term in pregnancy were 205 mg. per cent for cholesterol, 248 mg. per cent for phospholipid, and 353 mg. per cent for neutral fat. His highest value for neutral fat in pregnant women was 488 mg. per cent. Peters, Heinemann, and Man⁴ found a rise in lipids during pregnancy in which total and free cholesterol and phospholipids shared proportionately. Neutral fat rose proportionately far more than the other lipid fractions. In no instance, however, did the absolute values for neutral fat concentrations exceed the limits found in normal plasma.⁵ Records of excessive hypercholesterolemia and hyperlipemia in pregnancy have not been found in the literature, and the patient who is the subject of this report displayed at the end of her pregnancy an unexplained hyperlipemia of a degree which must be regarded as unique.

Case Report

Mrs. G. O., a 29-year-old multipara, came to the North Country Community Hospital on the evening of May 20, 1953, 18 days after the calculated term of a pregnancy which had been clinically uneventful and during which she had gained 20 pounds. On the day of her admission, she had developed generalized abdominal pain that gradually became localized in the epigastrium with radiation to the left shoulder. She had vomited once.

Examination revealed normal vital signs. She was uncomfortable but in no great distress. Moderate tenderness was noted in the epigastrium and in the left costovertebral angle. The uterus was at term. Rectal examination showed the cervix to be effaced, and a finger tip dilated, with the vertex deeply engaged below the spines. The membranes were intact.

The urine showed a faint trace of albumin, abundant acetone, but no sugar. In an uncatheterized specimen there were many white and red blood cells and an occasional fine granular cast. The red blood cell count was 3,340,000; the leukocyte count was 13,100. The creamy state of the blood which was first noted at this time prevented accurate estimation of the hemoglobin concentration.

The patient gradually went into active labor. About six hours before delivery, she developed intermittent attacks of dyspnea and orthopnea, without cyanosis, but with a temperature of 100.4° F., pulse of 90, respirations of 26, and a blood pressure of 160/90. Blood amylase at this time was estimated to have a value of 175 units (normal, 50 to 110 units).

*Chemical studies involved in this work have been aided by a grant from the U. S. Public Health Service and by gifts from Mrs. Katherine Lily Conroy.

With the aid of median episiotomy and elective low forceps she gave birth on May 22 to a living, full-term infant. Because of the ketosis and hyperlipemia, spinal anesthesia was employed. Blood loss was minimal, and the placenta was delivered intact without delay.

The blood coming from the episiotomy site had the appearance of cream of tomato soup. Samples for lipid studies were taken simultaneously from the vein of the mother and from the umbilical cord of the infant. Estimations of plasma lipids as made in the protein laboratory of the New York Hospital were as follows:

	MOTHER	CORD
Total cholesterol (mg./100 ml.)	1,800	65
Free cholesterol (mg./100 ml.)	1,065	21
Phospholipids ($P \times 25$) (mg./100 ml.)	2,180	108
Neutral fat (mg./100 ml.)	16,490	181
Total lipid (mg./100 ml.)	20,925	384

Following delivery, dyspnea, orthopnea, and epigastric pain persisted. X-ray examination of the lungs on the next day disclosed a left lower lobe atelectasis. For two days the temperature ranged between 101.4° and 102.2° F. The abdomen became progressively more distended until relieved by enemas and the evacuation of large soft green stools. On the first postpartum day an electrocardiogram was regarded as normal. Serum amylase was 155 units; carbon dioxide combining power was 32 volumes per cent; serum sodium was 119 meq.; serum chlorides 612 mg. per 100 ml.; serum calcium 8.2 mg. per 100 ml.; serum inorganic phosphate 2 mg. per 100 ml. On the second postpartum day the serum amylase was 97, and on the fourth day it was 51 units.

On the sixth postpartum day, the patient developed bilateral thrombophlebitis, and on the seventeenth day in spite of treatment with anticoagulants had symptoms indicative of a pulmonary infarction. During the next week, she improved rapidly. She was discharged from the hospital on the twenty-seventh postpartum day.

Lipid estimations repeated on the fourteenth postpartum day (June 5, 1953) and five months after delivery still showed gross abnormalities. High concentration of cholesterol persisted to the eighth month post partum.

	JUNE 5, 1953	OCT. 20, 1953	JAN. 21, 1954
Total cholesterol (mg./100 ml.)	746	345	302
Free cholesterol (mg./100 ml.)	235		
Phospholipid ($P \times 25$) (mg./100 ml.)	682	331	322
Neutral fat (mg./100 ml.)	1,203	1,550	
Total lipid (mg./100 ml.)	2,340	2,478	

On Oct. 21, 1953, studies were made of lipids in the blood of the patient's father, mother, and two sisters.

	AGE	TOTAL CHOLESTEROL (MG./100 ML.)	PHOSPHOLIPID ($P \times 25$) (MG./100 ML.)
Father	59	341	350
Mother	59	311	303
Sister	35	247	261
Sister	21	220	224

In addition to determinations of lipid constituents in the unfractionated plasma, observations were made in the Protein Laboratory of the New York Hospital on protein fractions obtained by means of Cohn's⁶ method No. 10. The techniques as they were employed at the New York Hospital have been described previously in some detail.⁷ In considering the results of these determinations, it must be emphasized that in the analysis of plasma in normal individuals and in a wide variety of pathologic conditions, the lipids are concentrated in two main fractions and that the lipids combined with alpha globulins as alpha lipoproteins are accumulated in Fraction IV+V+VI, and that those combined with beta globulins as beta lipoproteins are accumulated in Fraction I+III. Fraction II in which the proteins are, under normal conditions, chiefly gamma globulins contains almost no lipid. The results found in our patient at the time of her delivery and later are recorded in Table I. Comparable values for normal young women and normal women at the end of pregnancy are included.⁸

TABLE I. PROTEIN AND CHOLESTEROL FRACTIONATION OF PLASMA BY COHN METHOD No. 10 IN NORMAL NONPREGNANT WOMEN AND IN PATIENT WITH HYPERLIPEMIA

	NORMALS NONPREGNANT WOMEN AGED 18-35	NORMALS PREGNANT WOMEN AGED 20-39	MRS. G. O. AGED 29		
			MAY 22, 1953	JUNE 5, 1953	OCT. 20, 1953
<i>Protein.</i> —					
Total protein (Gm./100 ml.)	6.71 ±0.27	6.57 ±0.51	6.51	6.90	7.13
Fraction IV+V+VI (Gm./100 ml.)	4.83 ±0.25	4.17 ±0.32	2.19	3.61	4.86
Fraction II (Gm./100 ml.)	0.81 ±0.14	0.69 ±0.15	2.45	0.36	0.62
Fraction I+III (Gm./100 ml.)	1.34 ±0.13	2.05 ±0.24	1.87	2.98	1.65
<i>Cholesterol.</i> —					
Total cholesterol (mg./100 ml.) (Bloor Method)	189 ± 35	282 ± 62	2,140	749	350
Fraction IV+V+VI (mg./100 ml.)	61 ± 13	63 ± 18	15	22	59
Fraction II (mg./100 ml.)	3 ± 2	3 ± 2	1,895	2	4
Fraction I+III (mg./100 ml.)	123 ± 32	207 ± 58	231	725	286

Several extraordinary deviations from the values seen in normal nonpregnant and pregnant young women are apparent from inspection of the table. In the plasma studied at the time of delivery on May 22, the concentration of the protein found in Fraction II was more than three times the normal without increase in the concentration of the total protein. Furthermore, the hypercholesterolemia of 2,140 mg. per 100 ml. was distributed in a highly abnormal manner. In Fraction IV+V+VI which ordinarily contains the alpha lipoproteins, only 15 mg. was recovered. More surprising was the small amount of cholesterol recovered in Fraction I+III which in other hyperlipemic states has contained the bulk of the lipid, and the very large amount of cholesterol (1,895 mg. per 100 ml., or 88.5 per cent of the total) recovered in Fraction II which ordinarily contains almost none. These specific deviations were not apparent in the later studies of the plasma although the total concentration of cholesterol and its distribution never attained completely normal values.

Comment

Lipemia of high degree has been encountered in a variety of clinical conditions.⁹ It is found regularly in nephrosis; occasionally in the course of diabetes untreated with insulin; rarely in myxedema. It is an expected accompaniment of von Gierke's disease; it has been reported following thrombosis of the renal vein. It has been discovered on several occasions during the course of an acute pancreatitis. Other cases of hyperlipemia have been classified as essential or idiopathic. These patients appear to have a familial or hereditary defect in which there is a prolonged delay in the disappearance of the lipemia that normally follows the ingestion of fat. Their plasma is characterized by large accumulations of neutral fat with or without an accompanying hypercholesterolemia and hyperphospholipidemia. In such cases pancreatitis has been not infrequently a recurrent complication.

The degree of hyperlipemia has varied widely in the various conditions and in individuals with hyperlipemia of the same etiology. The highest value previously reported from any cause was recorded in 1864 by Speck¹⁰ who found total lipids of 17.4 Gm. per 100 ml. in a case of pancreatitis. The highest concentration of lipids in cases of essential hyperlipemia was reported as 9,476 mg. per 100 ml. by Buerger and Grütz¹¹ in 1932.

It appears that the degree of hyperlipemia encountered in our case exceeds any previously recorded. Its accompaniments are also noteworthy. Ketosis with acetonuria and reduction in alkaline reserve of the plasma were noted on the first examination and persisted until after delivery. The distribution of lipids was atypical. The relatively small amount of lipid in the form of alpha lipoprotein in Fraction IV + V + VI has been seen in other cases of hyperlipemia classified as nephrotic,¹² diabetic, or idiopathic. The paucity of lipid in Fraction I + III and its immense accumulation in Fraction II are unprecedented. The significance of the distribution of lipid as well as the excessive amount of protein found in Fraction II at the time of delivery is not apparent. Since the lipids were so concentrated in this fraction, the presence of lipid-bearing proteins is clearly indicated. Paper electrophoresis of the sample indicated no excessive amount of gamma globulins. The possibility that the excessive amount of neutral fat in the sample prevented effective separation of the proteins and permitted accumulation of beta lipoprotein in Fraction II cannot be denied. It may be stated, however, that in other cases of hyperlipemia no similar difficulty has been encountered.

In the excess of lipid, all fractions participated; cholesterol and phospholipid increased proportionately to about the same degree, which was approximately ten times the normal. The accumulation of neutral fat was much greater, and amounted to more than fifty times the average normal concentration. Less than a normal proportion of the cholesterol was esterified, and the free to total cholesterol ratio of 0.59 at the time of delivery may be compared with normal values approximating 0.30.

It is particularly noteworthy that the plasma of the infant was not demonstrably affected by the extraordinary hyperlipemia of the mother. It has long been known¹³ that the placental membrane offers an effective barrier to the passage of lipids, and that the lipid concentrations in the cord plasma are not only lower than the mother's, but are also much lower than in normal individuals in the nonpregnant state.^{3, 4} It may be emphasized also that the hyperglobulinemia in Fraction II of the mother was not reflected in the protein content of the infant, and that this was no higher than is often seen in other infants at birth.

The cause of the hyperlipemia in our patient was not discovered. Both the symptoms and the estimation of serum amylase supported a diagnosis of pancreatitis. Since, however, no clinical or chemical observations were made before the onset of abdominal pain, it is impossible to state whether the pancreatitis was caused by the hyperlipemia or whether its occurrence led to accumulation of neutral fat and other lipids in the plasma.

It is evident that the abnormalities in lipid metabolism did not terminate with pregnancy. For two weeks after delivery they were still evident to a marked degree. Even after a lapse of eight months the lipid relationships could not be regarded as normal.

The studies of the parents and siblings are of interest since they show that the cholesterol concentrations of the father, the mother, and one sister were higher than the usual normal values. This might indicate that the patient was a member of a hypercholesterolemic family. It does not explain the accumulation of neutral fat in her blood at the end of pregnancy.

Summary

A hyperlipemia of unprecedented degree developed in a previously healthy woman at the end of a normal pregnancy. It was signalized by the development of acute pancreatitis and was accompanied by nondiabetic ketosis. Its ultimate cause was undetermined. The infant, born during this episode, did not share in the hyperlipemia of the mother and showed no physical or chemical abnormalities.

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EVALUATION OF MALE BUFO AMERICANUS AND RANA PIPIENS FOR PREGNANCY TESTING*

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THE following study is an attempt to evaluate the use of male frogs and toads for pregnancy testing. Since Galli Mainini¹ introduced the male toad *Bufo arenarum* Hensel in 1947 as a reliable animal for the diagnosis of pregnancy, many workers employing Ranidae and Bufonidae have reported accuracies varying from 50 to 100 per cent.²⁻⁵ Analysis of these figures indicates that false negative reactions are the greatest source of error. These occur most frequently in very early pregnancies and in the latter half of gestation.

A satisfactory test for pregnancy must be accurate and also have the advantages of speed, simplicity, and economy. If such a test is based on the urinary excretion of chorionic gonadotrophin, the hormone levels in normal pregnancy and the sensitivity of the test animal must be known, as well as seasonal variation in sensitivity or any other factors which may affect it.

Our study is principally concerned with the male toad *Bufo americanus* and male frog *Rana pipiens*. Because the *Bufo americanus* was in short supply in the winter months, we have had limited experience with 500 male *Bufo marinus* toads and 500 male *Bufo woodhousii fowlerii*.

Rana pipiens

Sensitivity.—Because of the availability of this species work was begun with it, using over 5,000 frogs. The sensitivity of male *Rana pipiens* was determined with standard chorionic gonadotrophin† employing the method of Haskins and Sherman,⁶ in which it was shown that the time of appearance of sperm following injection of chorionic gonadotrophin was a hyperbolic function of the dose level from 22.5 to 100 I.U. It soon became apparent that the concentration of gonadotrophin was not the only factor which influenced the time of spermiation, as it was considerably delayed by temperatures less than 25° C. and toxic urines. Minor delays were caused by increasing the volume of fluid injected.

In an attempt to stabilize the effect of temperature, animals which were stored at 8° C. were brought to the laboratory 24 hours before being used, so that they could become accustomed to the higher temperature before injection. In this way a fairly uniform response was noted. If graded doses of hormone were plotted logarithmically against the log-time of response an essentially straight line graph was obtained (Fig. 1). Each point represents 20 animals.

*Aided by grants from the National Institutes of Health, U. S. Public Health Service (C-2054), and the James Hudson Brown Memorial Fund of Yale University.

†Purified chorionic gonadotrophin supplied by Parke, Davis & Company and Schering Corporation was restandardized on toads and frogs using the International Standard of chorionic gonadotrophin as a standard. The International Standard was supplied by Mr. Adley B. Nichols of the Pharmacopoeial Convention, New York, N. Y.

Although this method was rapid and proved accurate in a limited number of assays, it was too unstable for practical purposes. Dose-response curves employing percentage of reacting animals as an indicator of chorionic gonadotrophin concentration were then studied. If these values are plotted in the form of probits an essentially straight line graph is obtained (Fig. 2). For the present study, the estimated amount of chorionic gonadotrophin which produces 100 per cent response in these animals is noted in Table I. The effective dose 100 is approximately equal to twice E.D. 50. This approximation was checked with groups of animals using varying doses of standard chorionic gonadotrophin which were slightly less and slightly more than twice E.D. 50.

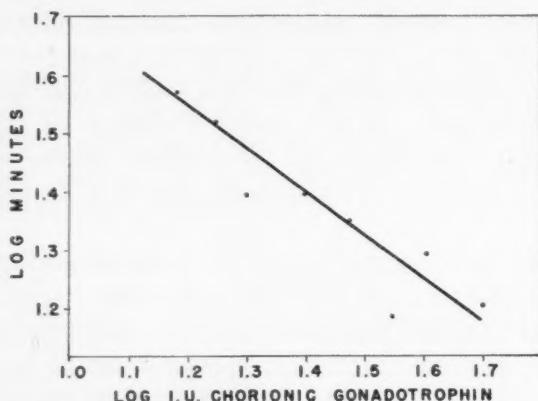


Fig. 1.—Sensitivity of male *Rana pipiens*, January, 1953. Log time of response plotted against log I.U. chorionic gonadotrophin (International Standard).

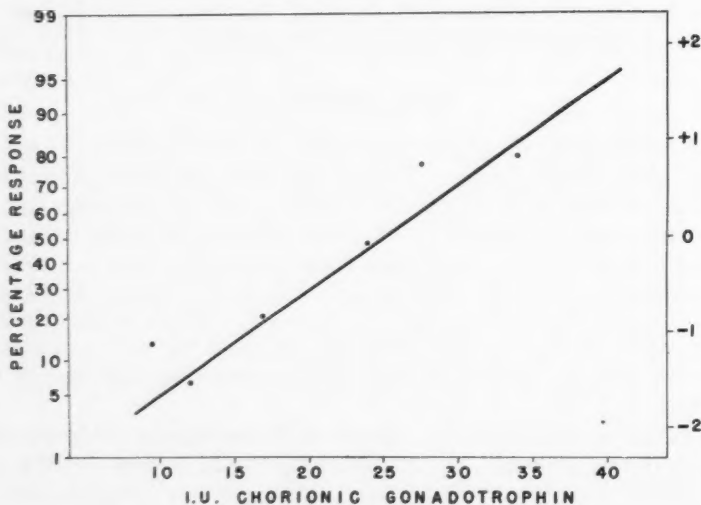


Fig. 2.—Sensitivity of male *Rana pipiens*, October, 1953. Percentage response plotted as probits.

Seasonal Variation.—Monthly sensitivities were determined on 75 to 100 frogs throughout the year and are recorded in Table I. These findings are comparable to figures reported by other workers.⁶⁻⁹

Specificity.—A limited clinical trial proved disappointing. In 69 patients who were subsequently delivered of normal infants, there was one false nega-

tive reaction; in 75 patients who were not pregnant, however, 19 false positive results were obtained. The majority of these occurred in the spring of 1953. Because of the frequency of false positive reactions, the cloacal fluid of 100 frogs was checked. No sperm were seen. They were then injected with distilled water and three hours later 12 of the 100 were found to have sperm in the cloacal fluid. In our experience, the high percentage of false positive reactions makes the male *Rana pipiens* unsuitable for the diagnosis of pregnancy, except perhaps in the late summer and winter when false positive reactions are less likely.

TABLE I. SEASONAL VARIATION IN SENSITIVITY OF *Rana Pipiens*

DATE		ESTIMATED AMOUNT OF C.G. REQUIRED TO GIVE 100% RESPONSE (I.U.)
1953	January	22
	February	22
	May	32
	August	80
	September	53
	October	50
	December	53
1954	January	60
	February	31
	March	44

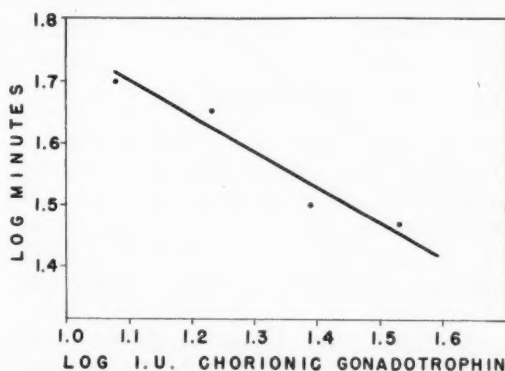


Fig. 3.—Sensitivity of male *Bufo americanus*, April, 1953. Log time of response plotted against log I.U. chorionic gonadotrophin (International Standard).

Bufo americanus

Sensitivity.—This species was chosen for more extensive study because in previous reports^{10, 11} no false positive reactions were noted. Over 2,000 male *Bufo americanus* toads were studied in a manner similar to that used in studying male *Rana pipiens*. Using time of response as an indicator of chorionic gonadotrophin concentration, a similar straight line graph was obtained (Fig. 3).

Since this method of assay using the male toad was subject to the same variability as that employing the male *Rana pipiens*, it was discarded in favor of dose-percentage response curves using probits. Again a straight line graph was obtained (Fig. 4).

Seasonal Variation.—The monthly sensitivity was determined with at least 100 to 150 toads except in the winter when this number was reduced to 50 to 60 because of limited supply. The estimated amount of chorionic

gonadotrophin required to give 100 per cent response is noted in Table II. E.D. 100 was computed in a similar manner to that described for *Rana pipiens*. It should be emphasized that the monthly sensitivities listed, while representative, will not be exactly the same from year to year.

TABLE II. SEASONAL VARIATION IN SENSITIVITY OF *BUFO AMERICANUS*

DATE		ESTIMATED AMOUNT OF C.G. REQUIRED TO GIVE 100% RESPONSE (I.U.)
1953	April	12
	May	13
	June	17
	July	24
	August	42
	September	45
	October	40
	November	36
	December	30
	January	25
1954	February	20
	March	17

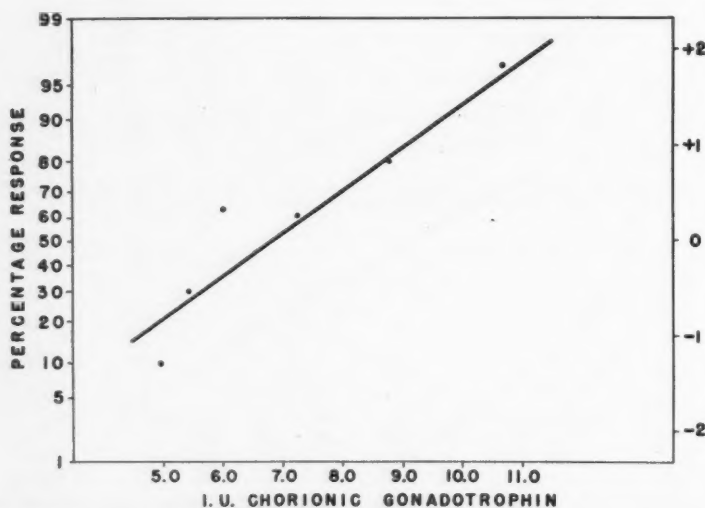


Fig. 4.—Sensitivity of male *Bufo americanus*, April, 1953. Percentage response plotted as probits.

Effect of Temperature.—With the same dose of chorionic gonadotrophin the time of response is relatively constant from 25° C. to 35° C., but at temperatures below 25° C. it is prolonged. In spite of this temperature variation, however, the percentage response remains constant. Table III contains the results of a limited experiment which demonstrates this. Galli Mainini reported similar findings with *Bufo arenarum* Hensel.¹

Weight of Toads.—Toads weighing between 30 and 50 grams are used for tests. Outside these limits a slight decrease in sensitivity with increase in weight is noted.

Re-use.—Toads which have given a positive reaction are re-used after resting two to three weeks. At room temperature (25° C.) sperm disappear from the cloacal fluid of positive animals in two to three days, but, if the animals are stored at lower temperatures, sperm may be present in the urine

three to four weeks following a positive reaction. It has been our custom therefore, to keep toads which are being used for routine testing at room temperature. Animals which have given a negative reaction may be re-used in two to three days, but we prefer to wait a week.

The sensitivity of toads which are used repeatedly in routine and experimental work, and are rested at least two weeks following use, does not appear to vary appreciably from that of unused animals at the same time of the year.

TABLE III. EFFECT OF TEMPERATURE ON TIME OF REACTION TO CHORIONIC GONADOTROPHIN

TEMP. (DEGREES C.)	NO. OF TOADS	AMOUNT OF CHORI- ONIC GONADO- TROPIN INJECTED (I.U.)	AVERAGE TIME OF RESPONSE (MINUTES)	RESPONSE (%)
20	10	25	87.0	100
24	10	25	68.5	100
26	10	25	64.6	100
28	10	25	62.5	100
30	10	25	62.5	100
35	10	25	60.6	100

Specificity.—In the experimental study of 2,000 toads, none was found with sperm spontaneously present in the cloacal fluid, nor were any false positive reactions noted in the course of over 2,000 routine tests for pregnancy nor following the injection of various types of eluants employed in experimental concentration techniques.

Husbandry

Sexual Differentiation.—The adult male toad varies in length from 54 to 85 mm. while the female is usually larger, 56 to 110 mm. The throat of the male is old gold to olive-ochre and contrasts sharply with the cream buff of the female. The male has a long-sustained, quite musical, rather high-pitched voice while the female is voiceless. In addition, the male has prominent excrescences on the inner-upper side of the first two digits and on the inner carpal tubercle.

Housing.—Wooden boxes or metal cages containing about 3 to 4 inches of 75 per cent soil and 25 per cent Spagnum moss mixture makes satisfactory storage for these animals. An ordinary bushel fruit box with a half-inch wire netting top will comfortably house 20 to 25 toads. They should not be overcrowded and each day the soil-moss mixture should be lightly watered so that it is thoroughly moistened without leaving standing water present. This is very important as toads desiccate rapidly. Animals which are currently in use should be stored at about 25° C.; those which are not in use may be stored to advantage at 10 to 15° C., as body wasting is less at this temperature.

Feeding.—Toads in routine use should be fed at least weekly. Mealworms provide a simple means of feeding. About 10 to 15 animals are placed in a clean netting-covered box and a handful of mealworms scattered around the bottom. If the toads are warm, they will be quite active and have no difficulty in catching the worms. If, however, the toads have been stored below this temperature they may be quite sluggish. To remedy this situation an ordinary goose-neck lamp containing a 100 watt bulb shining directly into the box will supply adequate heat. Toads are left in the box three to four hours at each feeding.

This method of feeding seems the most satisfactory. We have stored animals at temperatures ranging from 4° C. to 25° C. and used feeding

schedules ranging from no feeding at all to semiweekly feeding. Toads which are stored at 10° C. stay in fairly good condition if fed once every two weeks.

The husbandry of toads is important and unless they are in good physical condition deaths due to urine toxicity are much higher.

With the use of the husbandry methods just described, toads can be kept in good condition for five to six months. However, if a large number of animals are used it is difficult to prevent a fairly high spontaneous mortality rate. Because of the difficulty of maintaining a sufficient supply of toads throughout the winter, further study is being directed toward the finding of better husbandry methods.

Theoretical Considerations

In spite of seasonal variation in the test animal it should be possible to maintain the sensitivity of a testing system at any desired level by employing a concentration technique and varying the aliquot of urine concentrated, in accordance with the sensitivity of the animal at that particular time.

In pregnancy testing, however, concentration of urine containing no chorionic gonadotrophin but increased amounts of pituitary gonadotrophin may theoretically give false positive reactions.

The kaolin concentration technique described by Scott¹² and modified by us¹³ was used to check this aspect. Table IV lists the results obtained. One patient (N. S.) assayed 1,920 M.U.U. of follicle-stimulating hormone for 24 hours. Of 13 separate tests done with aliquots ranging from one to six hours, equivocal results (5 toads positive, 21 negative) were obtained. This is the highest reported value for follicle-stimulating hormone we have encountered. Because follicle-stimulating hormone levels of this magnitude must be rare, these experimental results were not considered to be of great clinical importance. From a practical standpoint, it appears that there is little danger of producing false positive reactions in toads if 3 hour aliquots of urine are used for concentration.

TABLE IV. CONCENTRATION OF URINE SPECIMENS CONTAINING ELEVATED F.S.H. LEVELS

PATIENT	F.S.H. CONTENT	ALiquot USED (HOURS)	RESULT
G. H.	384 M.U.U./24 hr.	6	Negative
H. K.	384 M.U.U./24 hr.	4	Negative
A. B.	624 M.U.U./24 hr.	4	Negative
E. M.	192 M.U.U./24 hr.	4	Negative
N. S.	1,920 M.U.U./24 hr.	4	Equivocal*
D. P.	Menopausal	4	Negative
— P.	Menopausal	4	Negative
— M.	Menopausal	4	Negative
— H.	Menopausal	4	Negative

*See text.

In much of the recent literature excretion of chorionic gonadotrophin is reported in international units per 24 hours. Since this is a more accurate indicator of excretion than concentration per liter, timed aliquots of 12 or 24 hour specimens should be more satisfactory than arbitrary volume designations which may represent vastly different periods of collection time.

As laboratory standards of comparison, the Aschheim-Zondek mouse and Friedman tests were used. The particular strains employed usually gave a positive reaction with urines containing more than 750 I.U. per 24 hours (i.e., about 0.5 I.U. per milliliter, assuming a urinary output of 1,500 ml. per 24 hours).

Chorionic Gonadotrophin Levels

One hundred nineteen quantitative urinary chorionic gonadotrophin determinations done on patients with normal pregnancies are shown in Fig. 5. For this work the male toad, *Bufo americanus*, and male frog, *Rana pipiens*, were used employing dose-percentage response on a probit scale. These figures are in substantial agreement with those of previous workers (Table V).

TABLE V. URINARY CHORIONIC GONADOTROPHIN LEVELS IN NORMAL PREGNANCY

	GESTATION PERIOD	URINARY GONADOTROPHIN (I.U./24 HR.)
Albert and Berkson ¹⁴	24-40th day	About 5,000
	60-70th day	Peak about 500,000
	Remainder	8,000
Loraine ¹⁵	90th day until end of pregnancy	4-11,000

It is evident that if a test is to be capable of establishing the presence of pregnancy any time from the tenth day after the first missed period to the end of gestation it must be sensitive enough to detect approximately 2,000 I.U. per 24 hours, otherwise false negative results will be obtained. In the various disturbances of pregnancy such as incomplete, inevitable, or missed abortions and ectopic pregnancies, chorionic gonadotrophin titers may be even lower. If such a condition is to be diagnosed, a test must be more sensitive and should be able to detect an excretion of 750 to 1,000 I.U. of chorionic gonadotrophin per 24 hours.

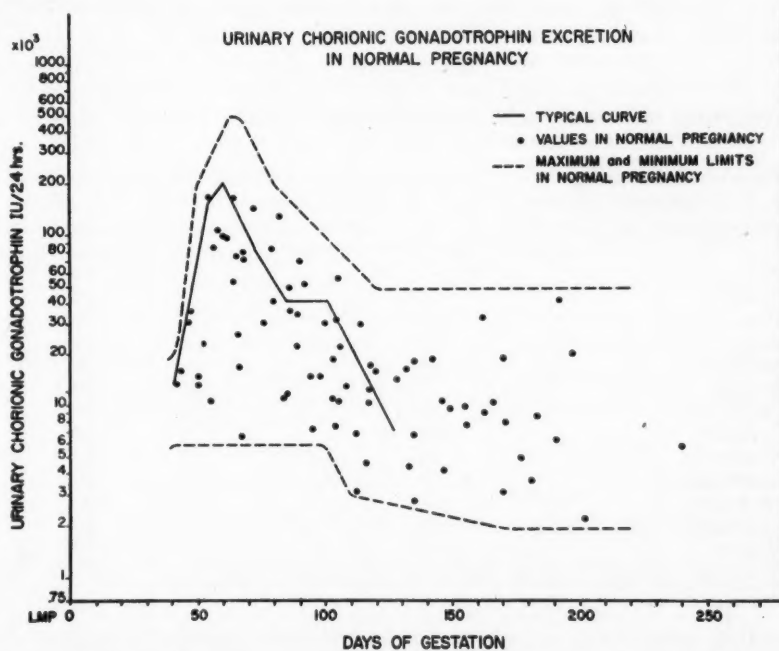


Fig. 5.—Graph of 119 quantitative urinary chorionic gonadotrophin determinations done on normal pregnant patients. Maximum and minimum levels, as indicated, are based on our experience as well as on values reported in the literature, but these may not represent final limits.

Because some animals which do not give a positive reaction to an injection of unconcentrated urine may represent false negative reactions, an appropriate amount of urine should be concentrated whenever negative reactions are obtained.

Materials and Methods

Urine Specimens.—An untimed morning or random specimen is acceptable for the diagnosis of pregnancy, but where quantitative estimations are required, a 12 or 24 hour specimen is necessary.

The patient is placed on restricted fluid intake during the collection period. There is no need to suspend medication and the presence of blood in the urine does not appear to be detrimental.

Preparation.—Unless the urine contains large amounts of particulate matter requiring filtration, it may be injected without any treatment whatsoever. Should the specimen prove toxic to the toad, about 25 ml. of the specimen is placed in a cellophane sac made by securely tying both ends of the cellophane tubing* and dialyzed for 20 to 30 minutes under running water. If undialyzed urine specimens are used, the loss from toxicity is 10 to 15 per cent, while with dialyzed urines it is 2 to 3 per cent.

Concentration Techniques.—A simple, rapid kaolin adsorption technique employing adsorption of chorionic gonadotrophin from buffered urine, and elution with sodium hydroxide is used. The details of this method are described elsewhere.¹³

The amount of urine to be concentrated depends upon the seasonal sensitivity of the toad, the level of chorionic gonadotrophin to be assayed, and the volume of the 12 hour specimen.

Table VI indicates the timed aliquot necessary to give a toad system sensitivity of 750 I.U. of chorionic gonadotrophin per 24 hours.

From Table VI it is evident that 50 per cent of the entire first morning specimen may be concentrated for each toad and seasonal variation in sensitivity disregarded if qualitative diagnosis only is required and if the first morning specimen is at least a 6 hour aliquot. During the spring it may be advisable to concentrate only 25 per cent of the first morning specimen per toad, thus reducing the theoretical possibility of false positive reactions.

TABLE VI. SENSITIVITY-ALiquOT TABLE BASED ON A TOAD SYSTEM SENSITIVITY OF 750 I.U. URINARY CHORIONIC GONADOTROPHIN PER 24 HOURS

DATE	REQUIRED C.G. CONTENT OF ALIQUOT* (I.U.)	APPROXIMATE ALIQUOT PER TOAD (MINUTES)
1953 April	24	40
May	26	50
June	34	70
July	48	90
August	84	170
September	90	180
October	80	160
November	72	140
December	60	120
1954 January	50	100
February	40	80
March	34	70

*Allowing for 50 per cent loss of C.G. in concentration procedure.

The monthly sensitivity of these toads will vary some from year to year so the aliquots listed are intended as examples rather than absolute values.

Testing System.—In order to maintain a sensitivity which is about equal to that of our colony of A-Z mice (i.e., capable of detecting 750 I.U. of urinary chorionic gonadotrophin per 24 hours) at all seasons of the year it is necessary to recheck all specimens which give a negative reaction with 5 ml. of

*70160A E53 Cellophane tubing 1.77 inches wide. Central Scientific Co.

original urine by a concentration technique. Positive reactions obtained from this initial step are considered conclusive. Such a system obviates concentrating all specimens. However, in cases where an urgent diagnosis is required, the specimen may be concentrated without this preliminary scouting procedure.

In actual practice, about 4 to 6 per cent of specimens which give an initial negative reaction give positive reactions when concentrated. These are usually from dilute specimens or very early or late pregnancies.

Test Methods.—

1. A drop of cloacal fluid is removed from each of two toads with separate fine-tipped (about 1 mm. in diameter) medicine droppers, placed on a clean slide, and checked for spermatozoa.

2. Five milliliters of urine or one-half of the eluate obtained by the concentration technique is injected into the dorsal lymph sac. This can best be done with a 3½ inch, 22 gauge needle, the point of which enters the gastrocnemius of the animal, then follows along the thigh and across the lower back until the midline is reached. If this site is chosen for injection, leakage is minimized.

3. At intervals of one hour following injection the animals are checked for spermatozoa. If both animals are positive at the first check the test is conclusive and read as "positive." If only one is positive the test is allowed to run four hours. Two positive animals at the end of this time constitute a positive reaction. If only one is positive the test is inconclusive and should be repeated. If both animals are negative the test should be repeated using concentrates of the appropriate amount of urine (Table VI).

Results

A total of 816 tests for pregnancy were done with the male toad. Seventy-three patients had incomplete clinical follow-ups and 91 cases of disturbed pregnancy will be considered elsewhere.¹⁶ The results of 497 routine pregnancy tests, 102 tests on patients in the latter half of gestation, and 53 non-pregnant patients will be discussed. Of the 497 routine pregnancy tests, A-Z mouse or Friedman correlation is available in 432.

TABLE VII. NORMAL PREGNANCY

TOAD SYSTEM			A-Z MOUSE TEST			FRIEDMAN TEST		
POS.	NEG.	ACCURACY	POS.	NEG.	ACCURACY	POS.	NEG.	ACCURACY
144	0	100%	99	1	99%	145	0	100%
145	0	100%						
289								

TABLE VIII. PREGNANCY, SECOND AND THIRD TRIMESTER

NO. OF PATIENTS	TOAD POSITIVE	CONC. TOAD POSITIVE	ACCURACY
102	98	4	100%

TABLE IX. NOT PREGNANT

TOAD SYSTEM			A-Z MOUSE TEST			FRIEDMAN TEST		
POS.	NEG.	ACCURACY	POS.	NEG.	ACCURACY	POS.	NEG.	ACCURACY
0	137	100%	1	115	99.2%	0	71	100%
0	71	100%						
208								

Normal Pregnancy.—Table VII indicates the results obtained on the urine of 289 patients who had normal pregnancies. Since ten days after the first day of the missed period is the time usually accepted for an A-Z or Friedman test to become positive in normal pregnancy, we have also adopted this standard and have accordingly omitted four experimental determinations which were obtained four days (2), six days (1), and seven days (1) after the missed period. In one instance both toad system and A-Z mouse were positive. Of the 289 cases only 10 required concentration of urine to give a positive result. Forty-four toad tests were not monitored with A-Z mouse tests.

In order to check the accuracy of the toad system in the latter half of gestation, 102 random specimens were obtained from patients in the second and third trimesters of pregnancy. The results are given in Table VIII, and emphasize the need for concentrating aliquots of urine whenever titers may be low.

Not Pregnant.—Of 208 patients studied for suspected pregnancy in whom the final clinical diagnosis was "not pregnant," the following results were obtained (Table IX). Twenty-one toad tests were not monitored with A-Z mouse tests. Not included are 53 random urine specimens from nonpregnant patients which also gave negative results.

From this rather small series it would appear that the toad system is as accurate as the A-Z mouse or Friedman test for the diagnosis of normal pregnancy. It should be noted that the accuracy given is for normal pregnancy and does not include disturbances of pregnancy which usually adversely affect accuracy figures. The correlation with the A-Z test was very high in our series of disturbed pregnancies.

Comment

Eighty per cent of the positive reactions are noted in less than two hours and all tests are conclusive at four hours. This short interval compares very favorably with the 96 hours and 48 hours required to read an A-Z mouse and Friedman test, respectively. The cost per toad test is considerably less than either of these tests and toxic urines are a much smaller problem since all specimens may be rapidly detoxified with the concentration technique.

The number of toads kept on hand at any one time should be about twice the number of pregnancy tests done each month. This allows for a resting period of two weeks between tests.

Under present husbandry and collecting conditions there is a shortage of male *Bufo americanus* in the winter months. This problem may be solved by improved husbandry methods and more extensive collecting in the spring and summer months when these toads are plentiful.

The *Bufo marinus* toads are obtained from Puerto Rico and are readily available throughout the year. They are currently being studied more extensively.

Male *Rana pipiens* are easily obtained and economical but the high percentage of false positive reactions is a distinct disadvantage.

Summary

1. An accurate, rapid, simple, economical system of pregnancy testing employing the male toad *Bufo americanus* is described.

2. Of a total of 652 tests reported there were 391 patients subsequently shown to have normal pregnancies and 261 nonpregnant women. In these cases the toad testing system gave an accuracy of 100 per cent. If four patients are included whose specimens were collected before the tenth day following the missed period the accuracy is 99.8 per cent.

3. A very high degree of correlation was present between the toad testing system and the A-Z mouse and Friedman tests.

4. The male frog *Rana pipiens* proved considerably less accurate as a test animal for the diagnosis of pregnancy.

5. The male frog *Rana pipiens* and male toad *Bufo americanus* show considerable seasonal variation in sensitivity.

We wish to thank Mr. James V. Massey, Jr., of the Fairfield Laboratories, Bridgeport, Connecticut, for his valuable assistance with the routine aspects of this study. Without the technical assistance of Patricia Bradt, Marion Brazel, Joan Crooker, Barbara Del Giorno, and Betty Weber this work would not have been possible.

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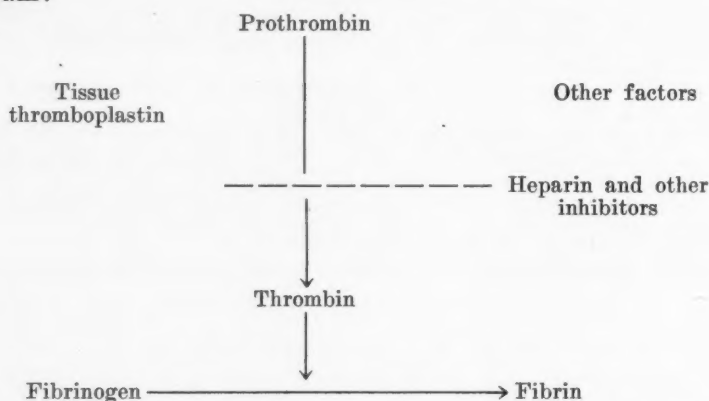
A STUDY OF CYTOFIBRINOKINASE AND FIBRINOLYSIN IN EXTRACTS OF TISSUE FROM HUMAN MYOMETRIUM, ENDOMETRIUM, DECIDUA, AND PLACENTA*

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A FIBRINOGENEMIA accompanied by massive hemorrhage in obstetrical patients has been reported by a number of investigators.¹⁻⁷ The condition has been observed primarily in cases of abruptio placentae, long-standing fetal death, and amniotic fluid infusion. The theory has been advanced that this afibrinogenemia is caused by an extensive intravascular clotting due to the infusion of thromboplastin-like material into the blood stream of the mother from the placenta, amniotic fluid, or decidua.^{2, 3, 5, 6}

Schneider⁶ has suggested for this condition a mechanism shown in the following diagram:



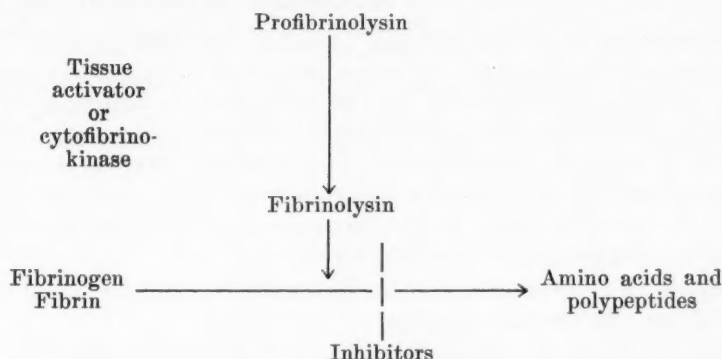
Although small thrombi have been found in the tissues of patients who have died from afibrinogenemia^{6, 8} these are not sufficient to account for all of the fibrinogen in the body. An intravascular clotting of such an extent as to remove most of this fibrinogen, i.e., 8 to 12 Gm., must of necessity be accompanied by a subsequent lysis of the clots.

In some cases of afibrinogenemia an accompanying fibrinolysin has been detected in the blood of the patient^{2, 7}; in other cases the investigators have been unable to demonstrate the presence of an active fibrinolytic enzyme system in vitro. It is suggested, however, that a fibrinolytic enzyme may be either partially or wholly responsible for the disappearance of the fibrinogen in spite of the fact that its presence cannot always be demonstrated in vitro by the methods in general use.

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A precursor of fibrinolysin (profibrinolysin) is present in all normal human blood plasma. This proenzyme can be activated by a number of factors including cytofibrinokinase (a tissue activator) and streptokinase (a bacterial activator). The active enzyme (fibrinolysin) thus formed is capable of hydrolyzing fibrinogen, fibrin, and certain other proteins. This may be represented by the following scheme:



For the fibrinolysin enzyme system to be important in these situations, the activating enzyme, cytofibrinokinase, must be found in the tissues involved, i.e., endometrium, myometrium, placenta, decidua. With the breakdown of the cells of these tissues as a result of catabolic and autolytic changes subsequent to menstruation, labor and the separation of the placenta, and long-standing fetal death, the intracellular cytofibrinokinase could initiate enzymatic conversion of profibrinolysin to fibrinolysin. When fibrinolysin is unopposed by inhibitors or antifibrinolysin, the hydrolysis of the body fibrinogen is rapid and dangerous. This mechanism has been suggested in previous papers.^{9, 10}

A comparable situation has been demonstrated by Tagnon¹¹ in cases of metastatic cancer of the prostate. He has reported fibrinolytic activity in the primary and metastatic cancer tissue and suggested that release of enzyme from this tissue was responsible for the hemorrhagic syndrome in his five patients. In his cases there was a deficiency of fibrinogen in the blood and a prolongation of the prothrombin time.

Margulis and associates¹² have reported fibrinolysin in 14 out of 17 uncomplicated pregnancies within the first 24 hours after delivery, with no change in prothrombin time, bleeding time, or clotting time.

The purpose of the work presented here was twofold: (1) the development of a more sensitive method for the detection of fibrinolysin *in vitro*, and (2) a study of the activation of profibrinolysin by the cytofibrinokinase contained in such tissues as myometrium, placenta, decidua, and endometrium.

The presence of such an activator would account for the fibrinolysin observed in obstetrical patients with both complicated and uncomplicated deliveries. A cytofibrinokinase in endometrium would give a mechanism by which menstrual blood remains fluid. Finally, such an activator would suggest an alternate method for the removal of fibrinogen from the blood stream of

patients suffering from obstetrical accidents in which tissue extracts may be forced back into the maternal circulation. The subsequent removal of fibrinogen by hydrolysis may then either be the principal cause of afibrinogenemia in these patients or may supplement the removal by fibrin deposition due to the presence of tissue thromboplastin.

Materials

Extracts from the myometrium, decidua, and placenta of 5 women who had had cesarean hysterectomies were prepared immediately after the operation and subsequently tested for fibrinogenolytic, fibrinolytic, and cyto-fibrinokinase activities. Results of similar extracts from one woman (M. H.) who had a therapeutic abortion and hysterectomy for carcinoma of the liver when approximately five months pregnant are also included as are those of a sample of placenta from a hysterotomy at sixteen weeks and samples of endometrium obtained after hysterectomy.

Tissue extracts were prepared as described by Tagnon¹³ and suspended and stored in 30 per cent sucrose solution.

Profibrinolysin was prepared by the method of Lewis and Ferguson¹⁴ using recalcified human plasma obtained from over-age blood from the blood bank. After precipitation at one-third saturated ammonium sulfate followed by dialysis the precipitate was dissolved in 0.01M phosphate buffer, pH 7.4, containing 0.9 per cent sodium chloride, to a volume one-tenth the original volume of plasma used and stored in the refrigerator.

Phosphate buffer at pH 7.4 in 0.90 per cent sodium chloride was used. In most cases 0.05M phosphate was employed. The proenzyme, however, was dissolved and stored in 0.01M phosphate.

*Bovine fibrinogen powder** was dissolved to a concentration of 2 per cent in phosphate buffer. Since this powder contains 42 to 48 per cent clottable protein, this solution will contain approximately 0.9 per cent fibrinogen. This solution was diluted 1:1 for determination of fibrinogenolytic activity or 1:10 for estimation of the fibrinolytic activity.

Commercial thrombin† (bovine origin) containing 1,000 National Institutes of Health units per milliliter was used.

Streptokinase‡ was dissolved in 0.05M phosphate to give a solution containing 10,000 units per milliliter.

Methods

Fibrinogenolytic activity has been determined by a method adapted from that used by Kunitz¹⁵ for the hydrolysis of casein by trypsin. Fibrinogen was substituted for casein, and streptokinase-activated fibrinolysin for trypsin in the preparation of standard curves relating optical density of the hydrolysis products measured at 280 m μ to units of fibrinogenolytic activity as shown in Fig. 1.§

The fibrinogenolytic activity of the tissue-activated fibrinolysin and of the tissue extracts alone can then be determined as follows:

*Armour Laboratories.

†Parke, Davis and Company.

‡Varidase from Lederle Laboratories.

§A fibrinogenolytic unit is defined as the activity which gives rise to an increase of one unit in optical density at 280 m μ per minute during digestion of 0.5 per cent bovine fibrinogen by streptokinase-activated human fibrinolysin under the conditions of the experiment.

Two tubes containing 0.2 ml. profibrinolysin, 0.2 ml. tissue extract, 0.6 ml. buffer, and 1 ml. of fibrinogen solution were prepared. In one tube the proteins were precipitated immediately by the addition of 3 ml. of 5 per cent trichloroacetic acid. The other tube was incubated for two hours at 37° C. before the reaction was stopped with trichloroacetic acid. After standing one hour the optical density at 280 $m\mu$ of the supernatant fluid was determined in a Beckman spectrophotometer. The fibrinogenolytic activity was then obtained from the difference in optical density of the two tubes by referring to the standard curve. The activity of the tissue extract itself was determined in the same way, omitting the profibrinolysin and substituting buffer to keep the volume constant.

The cytofibrinokinase activity of the tissue extract is the difference between the activity of the prolysin plus tissue extract and that of the tissue extract alone. The profibrinolysin solution itself showed no hydrolysis of fibrinogen in two hours' incubation.

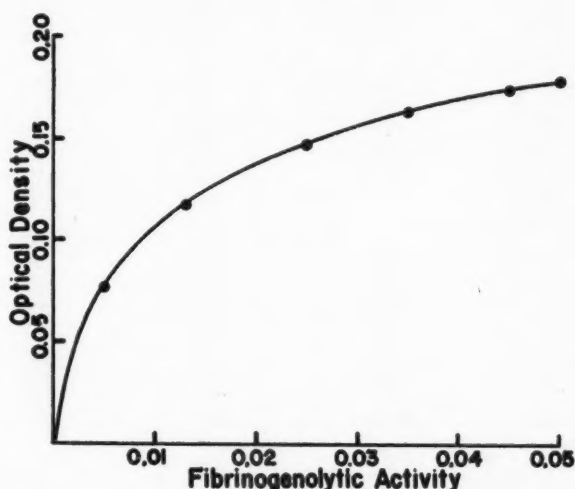


Fig. 1.—Calibration curve relating optical density of the trichloroacetic acid-soluble hydrolysis products at 280 $m\mu$ to units of fibrinogenolytic activity.

Fibrinolytic activity of the tissue-activated enzyme and tissue extract is determined by a method similar to that used by Tagnon¹³ and is reported in terms of the reciprocal of the time of lysis of a standard fibrin clot.

Results

Table I shows the fibrinogenolytic activity of the tissue extract, the profibrinolysin plus tissue extract, and the cytofibrinokinase activity as determined by the difference between the other two values. Of the tissues examined, all groups showed both fibrinogenolytic activity and cytofibrinokinase activity. Considerable differences exist, however, among the individual samples in each group. The high figures obtained with endometrial extracts are in agreement with those reported by Smith and Smith.¹⁶ It is of particular interest that endometrium in the secretory phase possesses greater activity than does that in the proliferative.

Table II contains figures showing the fibrinolytic activity of these same extracts. Significant fibrinolytic and cytofibrinokinase activity is demonstrated only in the extracts of myometrium and endometrium.

TABLE I. FIBRINOGENOLYTIC ACTIVITIES

TISSUE	PROFIBRINOLYSIN PLUS TISSUE EXTRACT		TISSUE EXTRACT ALONE		CYTOFIBRINO- KINASE
	OPTICAL DENSITY ($\times 10^3$)	UNITS* ($\times 10^3$)	OPTICAL DENSITY ($\times 10^3$)	UNITS* ($\times 10^3$)	UNITS† ($\times 10^3$)
<i>Myometrium.</i> —					
M. B.	60	3.3	29	1.5	1.8
M. C.	23	1.1	26	1.3	—‡
M. D.	29	1.3	19	0.9	0.4
R. G.	26	1.3	25	1.2	—
J. V.	32	1.6	25	1.2	0.4
M. H.	30	1.5	17	0.8	0.7
<i>Decidua.</i> —					
M. B.	57	3.1	23	1.1	2.0
M. C.	53	2.8	32	1.6	1.2
M. D.	61	3.4	44	2.3	1.1
R. G.	25	1.2	21	1.0	—
J. V.	22	1.1	23	1.1	—
M. H.	44	2.3	24	1.2	1.1
<i>Placenta.</i> —					
M. B.	49	2.6	40	2.0	0.6
M. C.	75	4.8	47	2.5	2.3
M. D.	47	2.5	45	2.3	—
R. G.	32	1.6	23	1.1	0.5
M. H.	47	2.5	49	2.6	—
16 weeks	82	5.6	48	2.4	3.2
<i>Endometrium, Proliferative.</i> —					
C. S.	50	2.7	38	1.7	1.0
E. A.	93	7.0	84	5.8	1.2
R. B.	124	14.4	59	2.9	11.5
G. G.	101	8.3	64	2.6	5.7
<i>Endometrium, Secretory.</i> —					
M. F.	134	18.5	103	8.7	9.8
M. M.	100	8.0	69	4.1	3.9
K. G.	221	90.0	141	21.5	68.5
<i>Fetal Tissue, M. H.</i> —					
Lungs	60	3.1	36	1.8	1.3
Liver	98	7.8	55	3.0	4.8
Brain	77	4.9	46	2.4	2.5

*Determined from optical density by use of calibration curve (Fig. 1).

†Determined by subtracting column 4 from column 2.

‡Where differences are within experimental error of the method the figures have been omitted.

The case histories of the patients who had cesarean hysterectomies contribute little to the understanding of the problem and therefore have been omitted. A short summary of pertinent facts about the patients from whom the endometrium was obtained may be of value, however; this information is shown in Table III.

Comment

As is evident from a comparison of Tables I and II a considerable difference is found between the *fibrinogenolytic* activity as measured by the optical density at 280 $m\mu$ of the hydrolysis products of fibrinogen, and the *fibrinolytic* activity as measured by the time of lysis of a standard fibrin clot.

Most of the extracts of each group of tissue showed ability to stimulate a fibrinogenolytic activity in the profibrinolysin, as well as the presence of an active proteolytic enzyme. On the other hand, only extracts of myometrial

TABLE II. FIBRINOLYTIC ACTIVITIES

TISSUE	PROFIBRINOLYSIN PLUS TISSUE EXTRACT		TISSUE EXTRACT ALONE		CYTOFIBRINO- KINASE
	TIME OF LYSIS IN MINUTES	UNITS*	TIME OF LYSIS IN MINUTES	UNITS*	UNITS†
<i>Myometrium.</i> —					
M. B.	105	0.95	600-1,320	0.10	0.85
M. C.	600-1,320	0.10‡	1,320	0.08	0.02
M. D.	240	0.42	600-1,320	0.10	0.32
R. G.	68	1.47	330	0.30	1.17
J. V.	1,320	0.08	1,320	0.08	—
M. H.	65	1.54	240	0.42	1.12
<i>Decidua.</i> —					
M. B.	600-1,320	0.10	1,320	0.08	0.02
M. C.	600-1,320	0.10	600-1,320	0.10	—
R. G.	600-1,320	0.10	1,320	0.08	0.02
J. V.	600-1,320	0.10	600-1,320	0.10	—
M. H.	600-1,320	0.10	1,320	0.08	0.02
<i>Placenta.</i> —					
M. B.	600	0.18	1,320	0.08	0.10
M. C.	600	0.18	600	0.18	—
M. D.	600	0.18	1,320	0.08	0.10
R. G.	600-1,320	0.10	1,320	0.08	0.02
M. H.	1,320	0.08	1,320	0.08	—
16 weeks	600	0.18	600-1,320	0.10	0.08
<i>Endometrium, Proliferative.</i> —					
E. A.	600	0.18	1,320	0.08	0.10
R. B.	150	0.67	1,320	0.08	0.59
G. G.	330	0.30	1,320	0.08	0.22
<i>Endometrium, Secretory.</i> —					
M. F.	120	0.83	600	0.18	0.65
M. M.	180	0.55	600	0.18	0.37
K. G.	60	1.67	120	0.83	0.84
<i>Fetal Tissue, M. H.</i> —					
Lungs	600-1,320	0.10	600-1,320	0.10	—
Liver	600-1,320	0.10	600-1,320	0.10	—
Brain	600-1,320	0.10	600-1,320	0.10	—

*Fibrinolytic units are expressed as the reciprocal of the time of lysis times 100 or $\frac{1}{T} \times 100$.

†Determined by subtracting column 4 from column 2.

‡An activity of 0.10 units is used as an approximation where lysis occurred between 600 and 1,320 minutes.

TABLE III. DATA CONCERNING PATIENTS FROM WHOM ENDOMETRIUM WAS OBTAINED

PATIENT	AGE	TYPE OF ENDOMETRIUM	DAY OF CYCLE	DIAGNOSIS
C. S.	43	Inactive proliferative	9	Endometrial polyps Metrorrhagia
E. A.	46	Proliferative	10	Menorrhagia Fibroids
R. B.	38	Proliferative	No period 2 months	Menometrorrhagia Fibroids
G. G.	32	Proliferative	11	Menorrhagia Fibroids
K. G.	38	Late secretory	34	Endometriosis
M. M.	35	Early secretory	21	Left ovarian cyst Irregular vaginal bleeding
M. F.	42	Secretory	26	Menorrhagia Fibroids

tissue and of endometrium were able to produce from the prolysin an enzyme capable of lysing a fibrin clot, and in only two of the uterine extracts and one extract of endometrium was sufficient active enzyme present to produce lysis in less than ten hours.

Whether this represents two different enzymes or a different mode of action on the two substrates it is impossible to decide at the present time. It is also recognized that while these methods provide a means of comparing the proteolytic and cytofibrinokinase activities of tissue extracts, they are not necessarily a direct measure of these quantities.

Regardless of the number of enzymes involved it has been demonstrated that extracts of placenta, myometrium, and decidua are all capable of hydrolyzing fibrinogen by themselves and in addition are able to activate the profibrinolysin which is contained in normal plasma. Schneider⁶ has clearly outlined mechanisms by which extracts of placenta or decidua may get into the maternal blood stream and Astrup¹⁷ has shown that entrance of tissue extract into the blood stream can activate the fibrinolytic system.

Lewis and Ferguson¹⁴ have tested a wide variety of dog tissue and found uterus (especially during pregnancy) and lung are among those having the greatest cytofibrinokinase activity, while good activity was found in fractions from pancreas, placenta, ovary (pregnant), brain, gall bladder and lymph gland. Their results and those of Tagnon have shown that this activity resides principally in the microsome fraction of the tissue extract. Numerous animal experiments have been carried out to demonstrate production of shock and defibrination by injection of such tissue extracts as placenta and lung. The effects have usually been attributed to thromboplastin infusion, while the fact has been overlooked that these same tissues are rich in cytofibrinokinase. It is suggested, therefore, that the removal of the fibrinogen from the blood stream in cases of abruptio placentae, long-standing fetal death, etc., may be due not entirely to entrance of thromboplastin into the blood stream but also, and perhaps to a much greater extent, to intravascular hydrolysis of fibrinogen by tissue-activated fibrinolysin. It may be that in the initial stages of the activation inhibitors of the fibrinolytic system are able to keep the enzyme under control. When these inhibitors are low to begin with or are used up to inactivate unusual quantities of active fibrinolysin, however, the system may then get out of control and hemorrhage may result.

The presence of a proteolytic enzyme and an activator of the fibrinolytic system in endometrium extracts helps to explain the fluidity of menstrual blood. Both of these activities apparently increase as the cycle progresses, reaching a maximum just before menstruation. A further study of these changes is in progress.

Summary

The presence of a fibrinogenolytic enzyme and a cytofibrinokinase has been demonstrated in extracts of human myometrium, placenta, decidua, and endometrium.

It is suggested that the presence of these enzymes may be partially or wholly responsible for the lack of fibrinogen which occurs in the blood stream of obstetrical patients under certain conditions, and in menstrual blood.

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CIRCULATION OF THE HUMAN PLACENTA

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TRANSLATION BY BRUCE A. HARRIS, JR., M.D.

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College of Medicine at New York City)

DESPITE extensive investigation, the circulation of the human placenta has never been completely clarified. Much of our ignorance stems from a failure to study the placenta in situ.

The Uterine Arteries and Veins.—

The major myometrial venous system (Fig. 1) is superficial, anastomosing extensively in the midline. This superficial system in turn drains a deep venous network which surrounds the amniotic sac. The branches of the deep network drain the placental site, *but do not communicate with the intervillous space except at the margin of the placenta.*

The main branches of the uterine artery (Fig. 2) form a superficial net running perpendicular to the long axis of the uterus. This net divides into two main systems. The first divides into capillaries which nourish the myometrium; the second embodies large vessels which pass through the musculature, penetrate the interstices of the venous net, and supply the placenta.

The Uteroplacental Arteries.—

According to previous authors, the uteroplacental arteries run within the placental septa. However, corrosion preparations of the placenta in situ demonstrate that nearly all the arteries empty into the intervillous space at the base of the individual cotyledons (Fig. 3). Only very rarely do arteries run within the septa. Moreover, the uteroplacental spirals are not predominantly located at the cotyledonary borders. Rather, they are distributed without regard to septal arrangement.

*First appeared in *Zeitschrift für Anatomie und Entwicklungsgeschichte*, 1936, published by Julius Springer, Berlin, Germany.

This particular paper by Rudolf Spanner has been selected as the first of a series for translation not only because of the basic importance of knowledge of placental circulation but because of the very careful and meticulous work here involved. Spanner's theory of overflow filling and marginal drainage has been widely accepted although not without some divergent opinion (cf., Ramsey, E.: *Contributions to Embryology* 35: 215, 1954; Hamilton, W. J., Boyd, J. D., and Mossman, H. W.: *Human Embryology*, second edition, Cambridge, England, 1952, W. Heffer & Sons, Ltd.). Essentially the argument does not disprove the findings of Spanner but seeks to place them in a proper relative position. This work will remain for many years to come the basis on which future exploration of placental circulation will rest.

L. M. H.

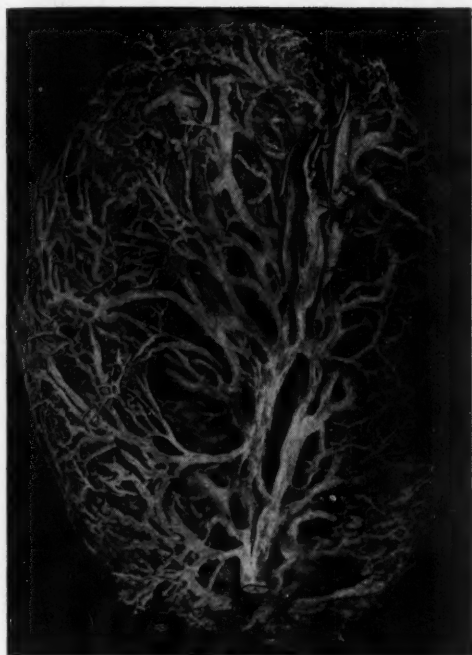


Fig. 1.

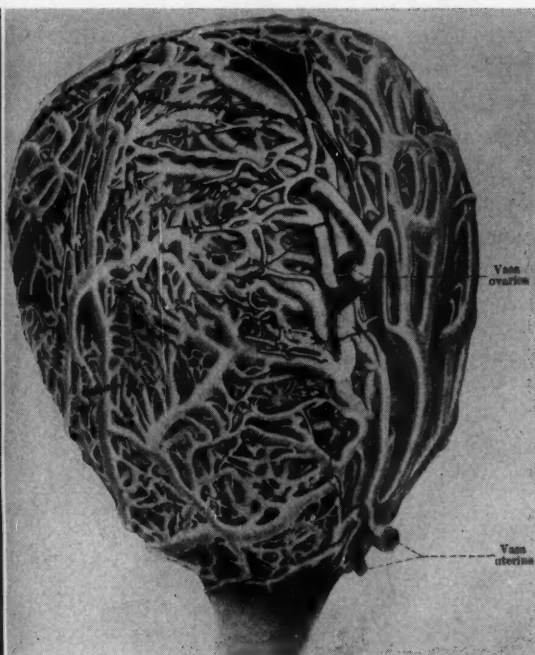


Fig. 2.

Fig. 1.—Seven months uterus. Corrosion preparation following venous injection.

Fig. 2.—Seven months uterus. Arteries dark, veins light.



Fig. 3.—Eight months uterus. Arterial spiral in the decidua, emptying into the intervillous space.

The arteries of the placental site are arranged in groups (Fig. 4). Each group is composed of a series of spirals, which branch out and have several orifices into the intervillous space. The number of orifices varies from one to nineteen, but the various groups of arteries are so close together that equal nutrition is assured to the entire placental surface.

The individual arteries may be divided into several segments. Immediately after passing through the inner venous net, the arteries undergo several gentle convolutions. They then divide, giving off markedly twisted branches. At their origin, these branches are about 1 mm. in diameter. Shortly, however, they undergo a fusiform swelling, increasing in diameter from 5 to 6 times. This dilated portion of the vessel acts as a reserve cylinder, and is capable of alterations in caliber. Beyond the reserve cylinder, the arteries subdivide into two or more lesser stems. Each of these emits blood through several openings into the intervillous space (Fig. 5).



Fig. 4.—Six months uterus. Corrosion preparation. View of the placental site from the uterine cavity. Observe the arterial spirals and their openings into the intervillous space.

In addition to their placental branches, the spiral vessels give off small branches which nourish the decidual plate. As an example of the number of branches, one of the author's preparations shows 39 arteriolar spirals. These terminate in 210 openings into the intervillous space and 107 decidual plate arterioles. The intervillous space arteries do not anastomose with those supplying the decidua. The vessels to the decidual plate divide into capillaries almost immediately after they originate. The venous drainage of the decidua empties into veins which by-pass the inner venous net.

The Fetal Vessels.—

Almost all the fetal vessels run perpendicular to the chorionic and decidual plates. The main villous branches run directly toward the decidua and then

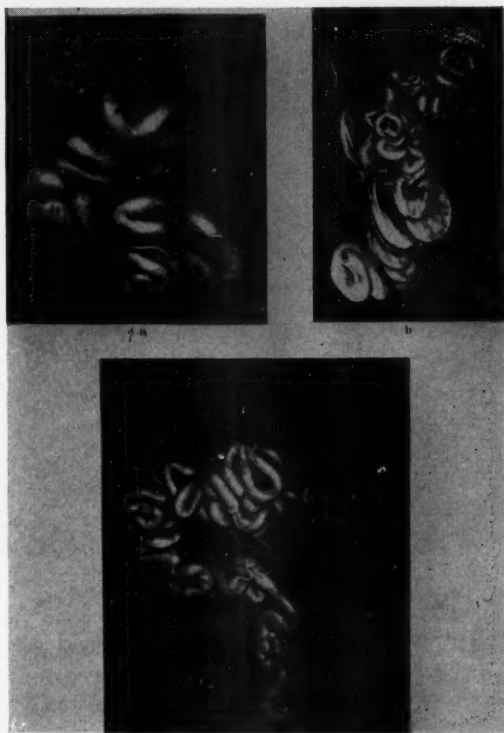


Fig. 5.—Isolated uteroplacental arterial spirals obtained by injection and a corrosion preparation.

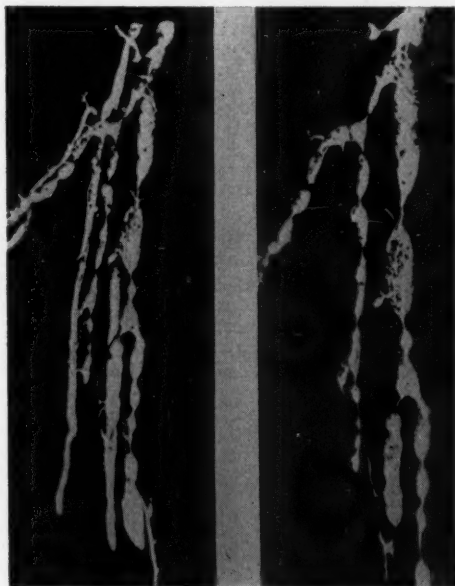


Fig. 6.—Fetal vessels in a small villous stem. *Left*, The artery is smooth, the vein beaded. *Right*, The stem after removal of the artery.

turn back, dividing into a large number of branches. These in turn subdivide, all the branches running parallel to one another and perpendicular to the placental surfaces. The manner in which they branch is reminiscent of an old-fashioned chandelier.

In that half of the placenta which lies nearer the chorion, the villous trunks do not ramify so extensively, although they follow the same general pattern. Finally, the villous stems immediately subjacent to the chorionic plate do not loop at all.

Microscopically, the fetal arteries are readily differentiable from the veins (Fig. 6). The injected arteries show a smooth surface without variations in caliber. The veins have a beaded appearance owing to the presence of sphincters. In the lesser veins the sphincters, which are composed of several layers of smooth muscle, lie next to the endothelium (Fig. 7). In veins of medium size, the sphincters are separated from the endothelium by a loose layer of connective tissue (Fig. 8). These sphincters regulate the outflow of blood from the villous stems.

A number of villous stems do not loop in the intervillous space, but descend into the decidual plate. These vessels run in the decidual plate for a short distance (choriodecidual vessels) (Fig. 9) before they return to the intervillous space.

The Placental Septa.—

Septa are not readily visible in the usual delivered placenta. These structures are best studied in placentas which have previously been injected and cleared.

The septa arise from the decidual plate. They are wider at the base and roughly triangular in frontal section. They run toward the chorionic plate, but stop short after having traversed two-thirds of the thickness of the organ. Fetal vessels never cross the septa, but may arise in one cotyledon, run in a septum for a short distance, and then return to the original cotyledon.

Injection of the maternal circulation shows that the individual cotyledons form circulatory units, demarcated by the septa (Fig. 10). However, because the septa do not traverse the entire intervillous space, there is a lateral overflow between the cotyledons at their upper (chorionic) portion. There are seldom less than 15 or more than 30 cotyledons in an individual placenta.

The Venous Drainage of the Placenta.—

A. *The Uteroplacental Veins of the Marginal Zone.*—The marginal zone is a peripheral strip 2 to 3 cm. wide. Sections in this area show the openings of numerous uterine veins (Figs. 11 and 12). Subjacent to the marginal area of the placenta there are multiple venous anastomoses. Communication between the veins of the myometrium and the intervillous space occurs in the decidual plate at the placental margin. Upon casual observation these communications may be overlooked because many of the veins contain placental villi (Fig. 13). The veins draining the intervillous space are always large, measuring 3.2 mm. at a maximum.

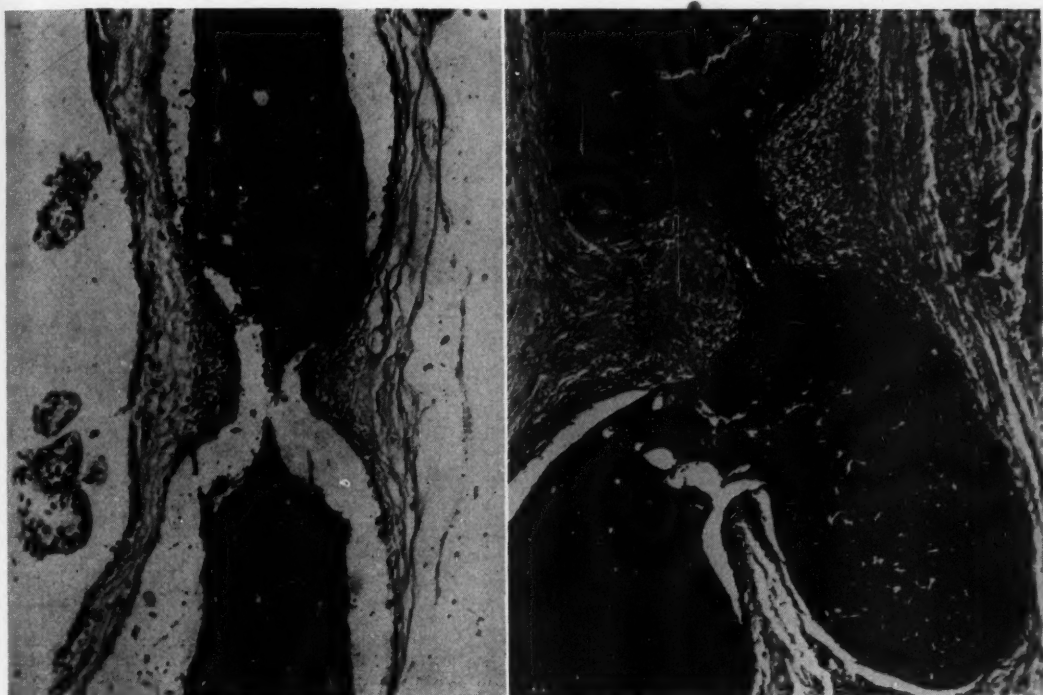


Fig. 7.

Fig. 8.

Fig. 7.—A vein from Fig. 6. Observe the sphincter. ($\times 133$; reduced $\frac{1}{5}$.)

Fig. 8.—Section through a medium-sized vein to show the sphincter.

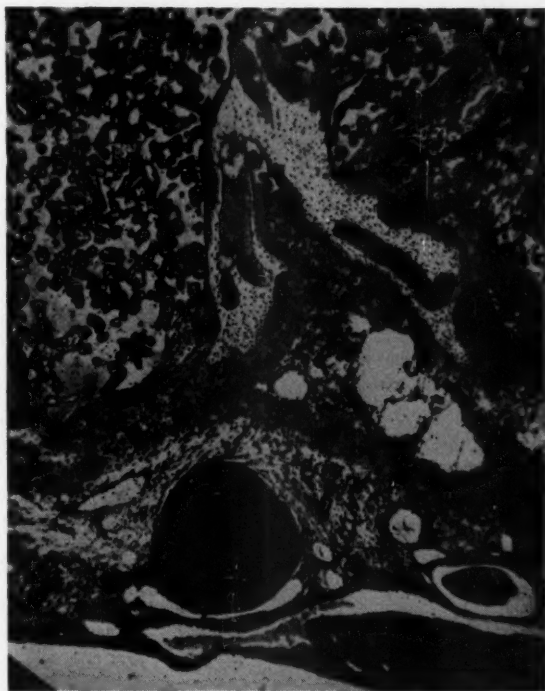


Fig. 9.—Basal portion of a term placenta. A major villous trunk is ramifying in the decidua. Below, a large fetal choriodecidual vessel.

The marginal veins differ notably in appearance from the uteroplacental arteries. The veins have no reserve cylinder as do the arteries. Moreover, the walls of the veins communicate with the intervillous space by way of numerous lateral perforations.

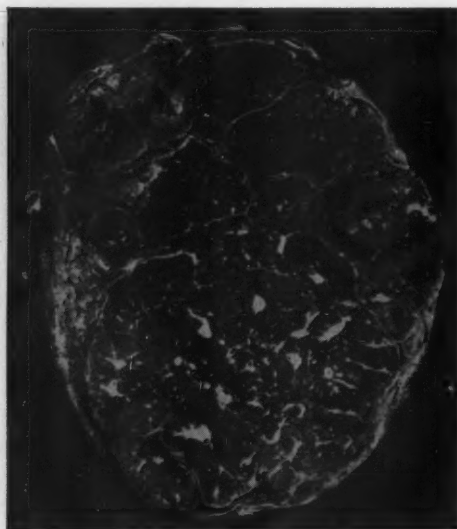


Fig. 10.—Frontal section of a delivered placenta. Twenty-six cotyledons are seen, divided by septa.

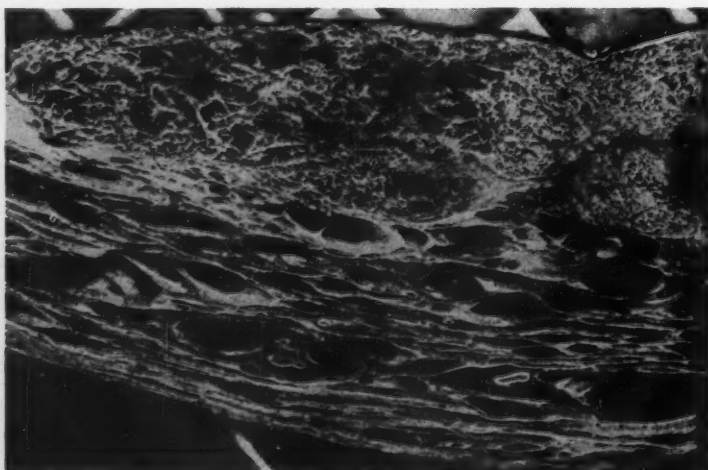


Fig. 11.—Section through the marginal zone. Note the size of the veins draining the intervillous space.

In both the marginal zone and the subchorial space, the villi are more sparsely distributed than in the decidual portion of the placenta (Fig. 14). This paucity of villi actually makes the marginal zone a continuation of the subchorial zone, and serves to promote blood flow into the marginal area. In the myometrium below the placental margin, the large veins communicate directly with the placental site (Fig. 16). Venous drainage into the decidual plate occurs in no other portion of the placenta. In regions remote from the placenta, the

large veins never extend into the decidua. In investigating ten placentas in situ, as well as a number of fresh specimens, I never observed veins communicating with the intervillous space more than 3 cm. from the placental margin

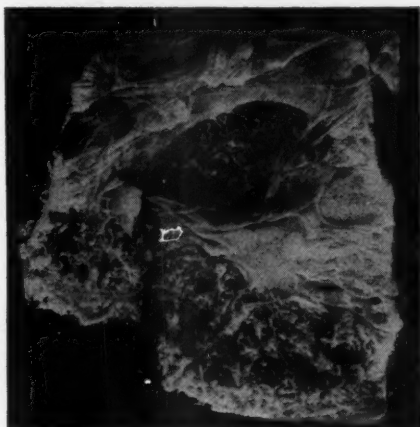


Fig. 12.—View from above of a 9 mm. opening between a vein and the intervillous space.

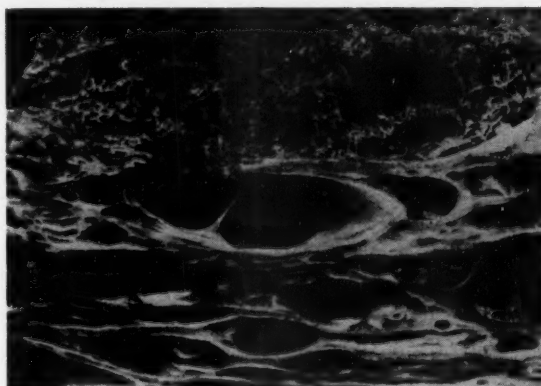


Fig. 13.—A massive opening between a marginal vein and the intervillous space.

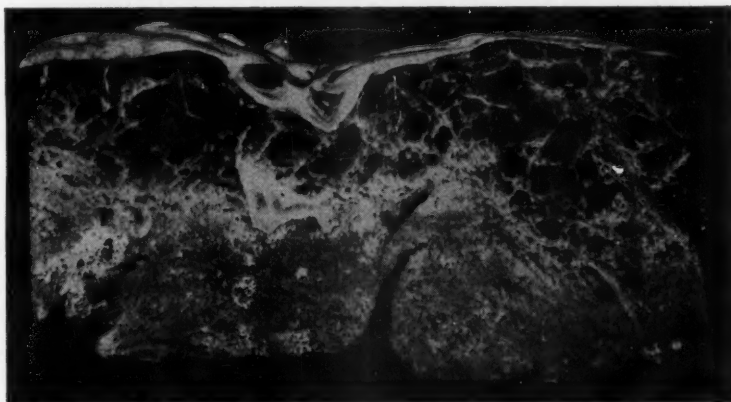


Fig. 14.—Newborn placenta, injected with tallow and extracted with chloroform. Note the sparse distribution of the villi in the upper third of the organ.

except in one case. I felt that this did not represent an unusually broad marginal zone, but rather the persistence of a more primitive type of drainage.

There is a striking development of the deep venous drainage system at the placental margin (Fig. 17). Sections of the myometrium in this area show as many as 31 venous openings over 14 cm. of perimeter. This would amount to about 100 venous openings in the entire marginal zone. The openings have an average diameter of 2.4 mm. They are reinforced by trophoblastic and fibrinoid masses.

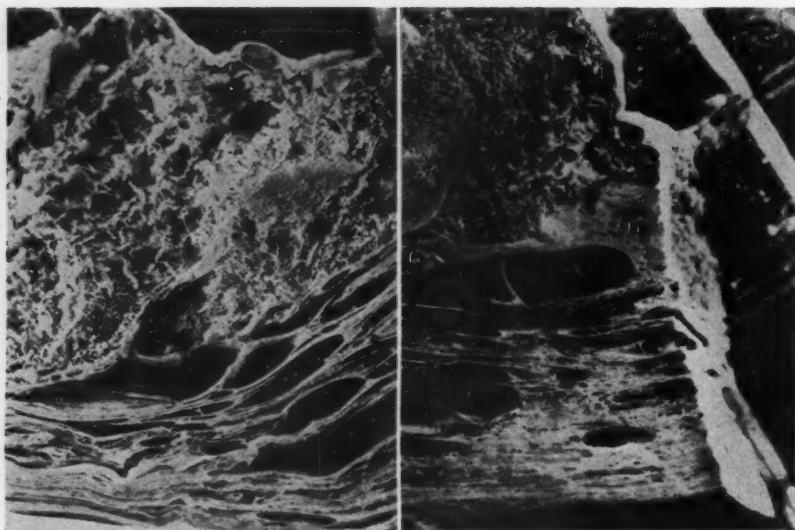


Fig. 15.

Fig. 16.

Fig. 15.—Marginal zone of a 7 month placenta in situ. A major villous trunk is encroaching on a vein and is fused with the vein margins.

Fig. 16.—Marginal zone. In the depths of the large vein, a villous mass is visible. The vein is traversed by a partition containing muscle fibers.

The decidual arteries and veins are differentiable in several ways. The veins do not spiral. The arteries enter the intervillous space by individual perpendicular branches, whereas the veins pass directly beneath the intervillous space and communicate with it by orifices in their walls. The venous orifices vary, depending on the degree of trophoblastic encroachment.

B. The Marginal Sinus.—The marginal sinus is a modified portion of the intervillous space, showing considerable variation. In different preparations, the marginal sinus may appear to be walled off completely or to communicate freely with the intervillous space.

Removal of the chorionic wall of the marginal sinus gives a good view of this vessel. The medial wall of the sinus may be perforated by numerous large venous openings (Fig. 18). If the medial boundary of the sinus is absent, it may be replaced by a trophoblastic mass, rich in fibrinoid material. The inferior wall of the sinus opens into the uterine veins. At various points, trophoblastic projections divide the sinus into upper and lower, or medial and lateral portions. These partitions, as well as the naked villous trunks which

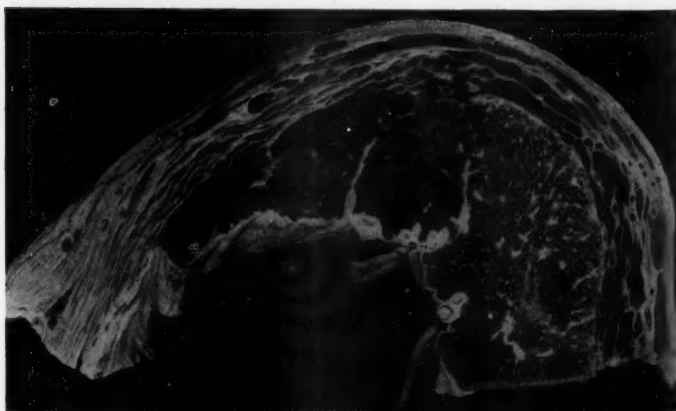


Fig. 17.

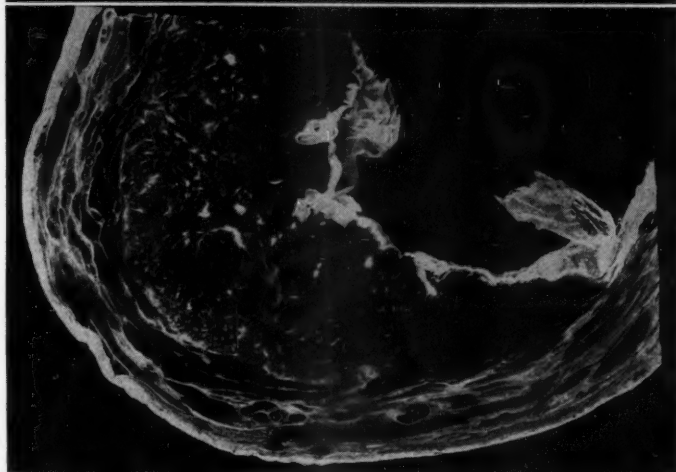


Fig. 18.

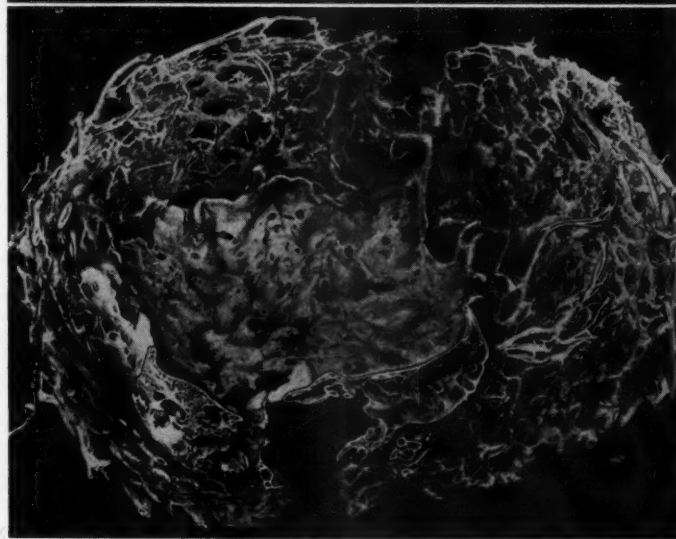


Fig. 19.

Fig. 17.—Eight months uterus, placenta in situ. Carmine gelatin injection. Observe the subchorial blood space and the marginal sinus. The latter is separated from the intervillous space by a septum.

Fig. 18.—Eight months uterus. Placenta in situ. The large marginal sinus communicates freely with the subchorial blood space and the intervillous space.

Fig. 19.—Three months uterus. Corrosion preparation. Venous injection fills the margin and the subchorial blood space, but not the central portion of the placenta.

traverse the sinus, serve to stiffen its walls and hold it open. The width of the marginal sinus is from 0.5 to 1.2 cm. Such a large sinus should play an important role in the venous drainage of the placenta.

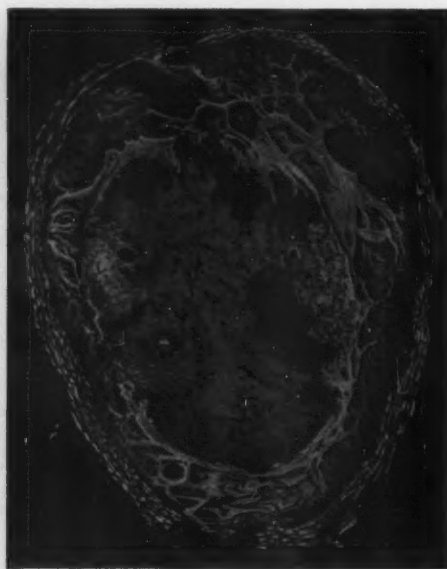


Fig. 20.—Seven months uterus. Corrosion preparation. The veins of the uterus were injected. Only the marginal sinus, the marginal zone, and a portion of the subchorial blood space show filling.

Examination of uteri with the placenta in situ shows that the marginal sinus constitutes the principal venous drainage of the placenta. Even in a three months pregnant uterus the venous drainage occurs almost exclusively in this area (Fig. 19). I injected a 7½ months pregnant uterus (with placenta in situ) through the arteries and veins, using solutions of different color (Fig. 20). Injections were carried out simultaneously at similar pressures. The arteries were injected with dark celluloid and the intervillous space was found to be filled with this material. A white injection mass was used for the uterine venous system. White material appeared only at the periphery of the intervillous space.

The Design of the Intervillous Space.—

The intervillous space may be divided into three portions, depending upon the degree of density of the villi. The basilar two-thirds contains many more villi than the upper portion (Fig. 15). This upper portion, or subchorial blood lake, contains far fewer fetal elements. It in turn makes up about one-third of the thickness of the organ. Finally, numerous relatively villus-free spaces ("caverns") (Fig. 21) occur at random in the basilar portion of the placenta. These communicate directly with the subchorial blood lake.

The intervillous space of injected placentas was photographed against a background divided into four quadrants of known size. Measurements derived therefrom showed that the individual villi vary from 25 to 110 microns in diameter, and are about 30 microns apart. There are approximately 113 villi per square millimeter.

The large villus-free areas in the lower two-thirds of the placenta are not due to artifact, because the villi at the margin are loosely distributed rather than packed together. Because these areas are connected directly with the subchorial blood lake, the spaces appear to be concerned with venous drainage.

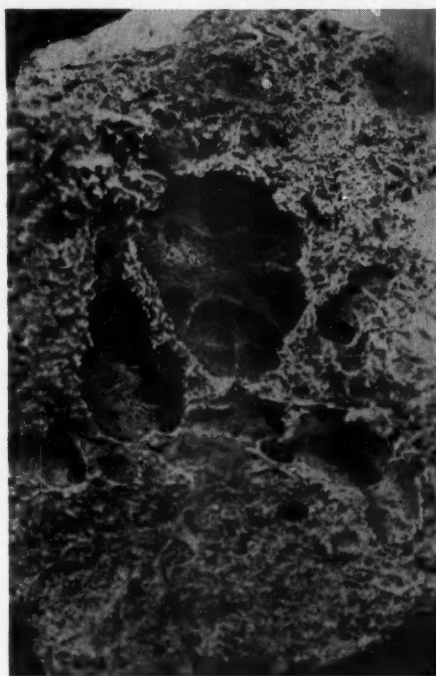


Fig. 21.—A "placental cavern" from the basal portion of a fixed and cleared placenta. This cavern communicates with the subchorial blood space.

In the delivered placenta, the subchorial blood lake is usually collapsed. Therefore, it has been partially overlooked. If the placenta is injected and cleared, an excellent preparation will be obtained. A great blood lake exists, communicating freely with the more compact basilar portion of the placenta and also, at the periphery, with the marginal sinus.

The Villous Circulation.—

The large villous stems have an artery and a vein surrounded by heavy connective tissue. On the outer surface of this stroma is a fine capillary network. The villi themselves have a loose stroma and present a dense capillary plexus with a few short transverse connections. At the base of each villus the vessels anastomose with the end branches of the arteries and veins of the major stems.

The villi may be fingerlike or club shaped. The former are narrow structures, frequently divided into daughter villi. The club-shaped villi contain massive capillary nets. Contrary to the findings of Stieve, there are no appreciable anastomoses between terminal villi.

The capillary network of the villous stems is connected with the central vessels by means of small, irregularly distributed channels. This network is richest in the chorionic third of the placenta, where arborescence of villi has

scarcely begun. It is probable that the capillary network of the stems does not contribute to the nutrition of the villous tree, but rather plays a secondary role in metabolic exchange between mother and child.

Theories of Maternal Circulation.—

The arteries supplying the uterus are so arranged as to deliver blood almost directly from the aorta. The uterine arteries are the principal branches of the hypogastric, and the ovarian arteries are direct branches of the aorta. The placental site is nourished by direct arterial branches which do not anastomose prior to their entry into the intervillous space. Moreover, the arterioles display a fusiform dilatation, then a marked narrowing just before they debouch into the placenta proper.

Thus, there is a reserve supply of blood, plus a mechanism for increasing the speed of flow, just prior to the entrance of blood into the intervillous space.

While the arteries are distributed over the entire decidual plate, the veins are confined to the margin. These marginal veins may be divided into two groups: the first drains the marginal sinus; the second, the marginal zone of the placenta.

According to my scheme, the blood enters the intervillous space basally and seeks the shortest route to the margin. The placenta is divided into cotyledons by the septa. These cotyledons form blood chambers which are open only at the top. Thus, blood entering the basal portion of a cotyledon must fill it to the top before overflowing. The blood streams in the individual cotyledons mingle in a subchorial lake and flow together toward the margin, hence to be drained into the veins in this area.

The Influence of Variations in Uterine Tonus.—

Uterine contractions have only slight effect upon the blood flow through the placenta. There is no proof that myometrial tonus normally is great enough to cause stagnation of the blood in the intervillous space.

I believe that contractions of the uterus may sometimes influence placental circulation unfavorably but do not completely prevent it. Thus, in the region of the marginal sinus, fibrinoid and trophoblastic support prevents any marked narrowing of the venous drainage channels. Furthermore, the veins are not connected to the intervillous space by a single branch, but rather by numerous lateral openings. I have observed smooth-muscle fibers in the chorion and the major vessels of the villous trunks. These, functioning together, help to regulate the size of the subchorionic blood space, and serve as a vasomotor regulatory mechanism for circulation in this area.

The Villous Pulse.—

Many authors have thought that pulsations of the chorionic villi assist in the propulsion of blood through the intervillous space. Under physiological conditions, however, the pulse wave in the umbilical artery is minimized before it reaches the small arterioles. It is thus no longer capable of producing rhythmical villous movement.

Sphincters are found in the medium-sized villous stems. These sphincters could obstruct the venous flow and cause gradual erection of the villi. This slight movement could have little effect upon the maternal circulation. On the other hand, it might favor metabolic exchange.

THE PHYSICIAN'S ROLE IN PREMARRIAGE COUNSELING*

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THE majority of today's practicing physicians have not fully accepted their responsibility as premarriage counselors. Most of them, through either lack of interest, reluctance to devote adequate time, or plain ignorance of technique, have limited their premarital examination to obtaining blood for a Wassermann test and dispensing a contraceptive method, either biological or mechanical. This approach to the young couple seeking premarital advice neither does justice to them nor adds credit to the medical profession.

Today's rapidly changing economic, social, and cultural conditions have added enormous strains to the institutions of marriage and family life. Of more than 30,000,000 married couples in the United States, at least one-fourth will end in the divorce court.¹ If one adds to these marriage failures the large number of unhappy homes as well as the frustrations and psychosomatic disorders which result from maladjusted marriages, the enormity of the problem can easily be seen. The awakening social consciousness of the population plus the need for gathering data and experience to cope with existing problems of marriage and family life have stimulated an ever-increasing number of physicians, sociologists, psychologists, ministers, lawyers, and educators to interest themselves in the field of marriage counseling.

The problems and techniques of marriage counseling may be divided for consideration into premarital and postmarital counseling. Premarital counseling is preventive or prophylactic. Postmarital counseling is therapeutic. One who desires to enter the therapeutic field of marital counseling, regardless of his professional background, must acquire specialized knowledge and experience in psychiatry, sociology, family law, and counseling techniques. However, the physician wishing to do premarital counseling is admirably equipped because of his broad medical and cultural education. In addition he needs only the attributes of personal warmth, sympathetic understanding, and an objectivity in approach to each patient's problems in order to succeed.

Ideally, premarital medical consultation should begin six weeks before the wedding² and should consist of the following:

1. A careful medical history including the previous sex history of both the man and woman. Inquiry should be made into possible hereditary problems in either family.

*Presented at a meeting of the Washington Gynecological Society, Jan. 22, 1955.

2. A complete physical examination should be done. Laboratory work should include a hemogram, urinalysis, Wassermann test, Rh factor determination, chest x-ray, and urethral and cervical smears and cultures as indicated. If the consulting physician does not treat males, they may be referred for a general history and physical examination as well as the indicated laboratory procedures.

3. Examination of each partner with a test such as the Sex Knowledge Inventory, Form X and Form Y, developed by Gelolo McHugh³ for Family Life Publications, Inc.

Form Y can do no more than measure the individual subject's knowledge of sex vocabulary and anatomy. It covers the basic facts of sex that experts believe are necessary to absorb effectively training in mental hygiene, human biology, or sex education. No prediction as to a particular individual's ability to adjust sexually can be made from his test score.

Form X, the Sex Knowledge Inventory for Marriage Counseling, was developed to help an engaged or married couple understand themselves and each other better regarding the meaning and uses of sex in adult life. It consists of eighty questions covering areas important for marriage counseling, and has an accompanying manual for the counselor which aids greatly in interpreting the answers. The areas covered are: (1) sex act technique, (2) the hymen, (3) possible causes of poor sexual adjustment, (4) sex dreams, (5) birth control, (6) sterilization and circumcision, (7) menstruation, (8) conception, pregnancy, and childbirth, (9) superstitions, misconceptions, and misinformation, (10) masturbation, (11) venereal disease, and (12) effect of the menopause on sex life.

Properly used, the Inventory can help free the couple from handicapping ignorance and unhealthy attitudes about sex. It is not intended as a measure of individual ability to establish a satisfactory sexual relationship, nor is it designed for making predictions about a couple's chance of success in their sex lives together. It is a counseling tool. Its successful use depends largely on the counselor. It is intended to ease his work and save his time by providing quickly a comprehensive picture of his counselee's sex knowledge and attitudes, pointing out those areas where counseling is most needed. The counselee's answers to specific questions will help the counselor to pick out specific points to be covered in later interviews, as well as gaining a general picture of the counselee's sex knowledge and attitudes. Several interviews spent in discussing the responses will serve to establish patient rapport as well as possibly to uncover deeper psychological and emotional problems which were unsuspected. In the latter event, referrals to a properly trained psychiatrist should be made.

4. A selected bibliography should be presented to the couple, advising books which most nearly suit their needs.

5. A very careful premarital pelvic examination should be done. According to Kinsey⁴ between 50 and 60 per cent of all women about to be married are virgins. Thus the commonest premarital pelvic finding is that of an intact hymen. A thick, rigid hymen may be treated in several ways.

With some patients it might be more desirable to give instructions for gradual manual dilatation of the hymen during the few weeks preceding marriage. In most instances, however, it is preferable for the physician during several weekly visits to dilate the hymen by the use of graduated dilators. This method, if gentleness is used, is nontraumatic and affords an excellent opportunity to teach the patient about her own genital anatomy. Hymenotomy is utilized by some practitioners but is less desirable than dilatation since the incision requires approximately three weeks to heal and frequently results in tender scar tissue which may contract enough that dilatation may eventually be required. Hymeneal dilatation or hymenotomy should never be performed without the knowledge and consent of both parties.

At the time of the premarital pelvic examination the presence of vaginal discharge, cervicitis, cervical polyps, condylomas, and other minor conditions should be noted and treatment instituted. Developmental defects which would interfere with normal sexual intercourse and reproductive life will be discovered and corrected. Uterine and ovarian tumors will be noted at the time of examination and proper disposition made before marriage. An estimate of the capacity of the bony pelvis can be made with the patient's future childbearing capabilities in mind. The knowledge that she possesses normal genital organs and an adequate pelvic capacity is most reassuring to the young bride-to-be. In discussing his findings, however, the physician should carefully avoid the use of such terms as "small pelvis," "infantile uterus," or "tipped womb."

6. Specific instructions in the use of the diaphragm should be given, if personal and religious views make this mode of contraception desirable. If not, the counselor should discuss the rhythm method and its application to child spacing. If the family, cultural, and religious background is such that the use of mechanical contraceptives would create feelings of guilt, the patient should be strongly discouraged in their use. Such feelings of guilt so generated could create new tensions, block mutual psychological adjustment, and prevent the development of proper emotional values in marriage.

7. The physician should offer such specific advice on lubricants, sexual and feminine hygiene, and coital procedure as is indicated by the sex knowledge tests and the counselee's questions.

The amount of time needed to be spent with each couple will vary considerably. Their questions and requests as well as the results of the sex inventory tests will help the physician evaluate their specific needs, interests, attitudes, fears, and sense of values.

Dr. Nadina R. Kavinsky⁵ classifies the bride and groom that one encounters in premarital counseling into four categories:

Group I.—This group is comprised of enlightened, healthy, sexually and emotionally mature individuals. They have been so well prepared for marriage at home, school, and church that the physician needs only to examine them, make a few simple explanations and clarifications, and supply reassurance.

Group II.—This group has primarily physical problems that the physician can discover at premarital examination and institute proper treatment.

Group III.—This group is comprised of the emotionally immature. Even though they may be mature physically, experienced sexually, and possess a broad educational background, their psychological and emotional attitudes toward marriage, life, and the solution of problems of everyday living may be distinctly immature. It is this group that needs more time and wise counsel in order to establish the basis of more healthy attitudes.

Group IV.—This group contains the seriously neurotic or psychotic men and women. It is here that may also be found alcoholics, drug addicts, and criminals. The physician should be on guard to recognize these conditions. Obviously, all patients in Group IV should be counseled only by one who has been psychiatrically trained.

Today, the physician is able to do valuable missionary work in preparing young people for marriage. As a prospective counselor for family and marital problems he is in an enviable position. The law in 34 states requires a physician's certification of freedom from venereal disease before a marriage license is issued. This annually represents an enormous reservoir of people who would benefit by premarital counseling. An increasing number of schools and colleges are including courses dealing with marriage and family living in their curricula. This plus an ever growing flood of information through lay journals is educating the public on what they should receive and can demand in premarital counseling. Even those who have not had any basic sexual or premarital education might feel the need for this information and will seek the family doctor for advice because of his position of respect and esteem in the community. Naturally some doctors consulted for premarital examination will have neither the interest nor the time to serve adequately in this capacity. It logically follows, then, that those doctors should refer the couple to someone who will supply complete and proper counseling.

One can only feel a great sense of obligation when it is realized how the individual physician can influence the quality of marriage in his community. He can directly influence marriages by: (1) adequate premarital and marital counseling, (2) lending his knowledge to aid in child spacing and family planning, (3) early discovery and treatment of venereal disease, (4) striving to improve medical and surgical gynecology, thus minimizing certain iatrogenic disorders which could unfavorably influence existing or projected marriages, (5) furnishing the community with obstetrical care which is of such quality that physical as well as psychic trauma from childbirth will be prevented.

Indirectly the physician can influence marriage and family living by assuming responsibility as a community leader and educator. It is my belief that he must participate actively with other community leaders such as ministers, teachers, lawyers, and marriage counselors in preparing and presenting programs for youth and parent education in the church, school, and home. Then, and only then, will the results be evident by a diminution in the numbers of maladjusted people who fill the divorce courts, criminal courts, and psy-

chiatric services of our hospitals. It is my belief that the physician meets most of the premarriage problems first and should train himself to supply adequate counseling. If he has no interest in the subject he should refer the couple to someone who has. If the prophylactic aspect of marriage counseling (i.e., proper sex education of the young and the premarital interview) becomes more widespread through the efforts of physicians and allied counselors, the burden of the therapeutic aspect (i.e., resolving conflicts of poor and unhappy marriages) will become greatly lessened.

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TRAUMATIC UTERINE SYNECHIAE: A COMMON CAUSE OF MENSTRUAL INSUFFICIENCY, STERILITY, AND ABORTION

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THERE IS much to be learned about the causes and the pathogenesis of amenorrhea. Recent progress in endocrinology has afforded many interesting data; current trends in gynecology indicate that further advance will result from hormonal research. Hormones and the concept of functional disorders, however, should not cause us to overlook other authentic lesions even though these may be rarer than hormonal imbalance, for example, or tuberculosis of the endometrium.

Several recent cases of intrauterine adhesions have been of special interest in their causal relationship to hypomenorrhea, amenorrhea, sterility, and repeated abortions. This paper embodies certain case reports and studies of the nature, causes, frequencies, signs, symptoms, treatment, and other aspects of secondary uterine adhesions.

CASE 1.—The following case, our first, led us to make our observations. Mrs. D. G., 32 years of age, sought advice in February, 1952, because she had had menstrual difficulty following a dilatation and curettage performed after an abortion two years prior to this date. Her past history had been normal. Menstruation began at the age of 15 years and was normal and painless. The patient had had three abortions. The course following the first two was uneventful. The third occurred at the third month of pregnancy in 1948, after which a curettage was required. The patient then had amenorrhea for six months, after which a poor monthly bloody discharge appeared preceded by pain and vomiting for two or three days.

From 1948 to 1952, this patient had received many forms of treatment including various hormonal injections, and even psychotherapy. All these treatments had been unsuccessful.

Pelvic examination disclosed no gross abnormality. When an endometrial biopsy was attempted synechiae were diagnosed; a Novak cannula could not be introduced further than a few millimeters. A first attempt to perform a hysteroqram was unsuccessful due to vaginal leakage. A second attempt with radiopaque medium showed only an intravascular (angiogram) outline; no uterine cavity was visible. A third hysteroqram was performed under general anesthesia. A thin metallic catheter was used to dilate the cervical canal. The uterine cavity on this radiogram appeared narrow and tortuous; when the radiopaque medium was injected under increased pressure, again an intravascular pattern appeared.

On Oct. 18, 1952, the thirteenth day of the menstrual cycle, an exploratory laparotomy was performed. The adnexa were normal and the uterus was slightly hypertrophied. After resection of the presacral nerve, hysterotomy was performed. The uterine cavity was found with a thin metallic catheter introduced through the cervix. Large fibrous muscular bundles had replaced the uterine cavity. These had to be cut. The cervix was dilated from above. Endometrial grafts were taken from a myomatous uterus removed simultaneously in the next operating room at the tenth day of the cycle; the patient was isogroup O, Rh

positive. The endometrium had previously been examined histologically and was also re-examined in the extirpated uterus. The endometrial grafts were then put into the uterine cavity of the first patient without any suture, after which the hysterotomy incision was closed with catgut.

Menstruation appeared on Nov. 22, 1952, and thereafter every month, lasting five days and was of normal amount and painless. In April, 1953, another hystero-gram showed that in spite of the good functional results a corporeal adhesion persisted. However, the patient became pregnant in October, 1953.

In this case of hypomenorrhea, diagnosis was markedly facilitated by means of hystero-graphy which revealed the unsuspected extent of synechiae confirmed by operation.



Fig. 1.—Confirmation of synechiae by hystero-gram in Case 2.

In some other cases clinical diagnosis is not possible without the help of hystero-graphy. An instance of such a case follows.

CASE 2.—Mrs. C., 41 years of age, sought advice because her menstrual periods were becoming more and more scant and were accompanied by hot flushes, palpitation, and dyspnea. During the last three years she had gained 18 pounds. All of these complaints would have seemed very common and probably due to the proximity of the menopause if it had not been for (1) the absence of early menopause in her family and (2) the history of therapeutic abortions. We learned with some astonishment that this woman who had and still wanted to have children had been pregnant three times, that the obstetricians of her country had decided during each pregnancy to perform a therapeutic abortion because she had a retroverted uterus. According to the husband, the obstetricians had feared incarceration of the uterus. The dilatations and curettages were done 8, 7, and 5 years previously. For the interruption of the third pregnancy a first dilatation and curettage was complicated by fever and hemorrhage and a second dilatation and curettage was followed by amenorrhea. In an attempt to overcome the amenorrhea, estradiol, progesterone, testosterone, and chorionic gonadotropin had been given to this patient. After one year, a very scant menstrual flow recurred and it was at this time that the chief complaints of the patient developed.

Pelvic examination showed a retroverted, retroflexed uterus with an enlarged right ovary, prolapsed into the posterior cul-de-sac. The cervical os was the size of a pinhead.

Suspecting uterine synechiae, we performed hystero-graphy which confirmed the diagnosis (Fig. 1). A dilatation and curettage was performed under general anesthesia, after which the two following menstrual periods were more abundant. In this case, the diagnosis suspected from the clinical history and findings was established only by hystero-graphy. Hysterometry had failed to reveal any abnormality.

CASE 3.—In a third case there was a history of repeated abortions. Hystero-graphy had been misinterpreted as showing a uterine polyp. Curettage was performed and another pregnancy terminated in miscarriage. Hystero-graphy was reinterpreted as showing synechiae.

Mrs. W. D. G., aged 25 years, had had three successive miscarriages at the third, fourth, and fifth month of pregnancy, respectively. She had also had previously an abortion by dilatation and curettage at the third month of pregnancy.



Fig. 2.—Hystero-graph in Case 3 showing synechiae that resembled uterine polyp.

Physical examination disclosed no detectable abnormality. We performed hystero-graphy in 1950 (Fig. 2). The hystero-graph was interpreted as showing the presence of a uterine polyp and a dilatation and curettage was performed. The patient became pregnant three months later. In spite of bed rest and stilbestrol therapy, the patient aborted during the sixth month of pregnancy. Three years later, during our studies on uterine synechiae, we asked the patient to return her hystero-graphs. At this time, we had no difficulty in interpreting the hystero-graph as showing uterine synechiae. These were considered as having been responsible for the four successive miscarriages.

We do not want to overburden this article with the history of 42 cases which we have observed during the last eighteen months. These cases enable us to describe a clinical picture of uterine synechiae characteristic enough to suggest the diagnosis. This must be confirmed by hystero-graphy, however, and we shall present sufficient radiographs to cover, we hope, the scope of this condition.

A short anatomical description is believed necessary to the understanding of the clinical and radiological features of uterine adhesions. Readers interested in this subject are referred to the articles we have published and the other references cited.^{1, 5, 7-24}

Pathology.—Synechiae result in a localized disappearance of the uterine cavity, which is filled by a normal or sometimes fibrous myometrium. Three types of synechiae can be described: (1) Synechiae of the corpus, cervix, and isthmus are very seldom encountered. It is exceptional not to find one or two

small vestigial cavities on serial sections of the uterus. (2) Corporeal synechiae are the most common. The uterine cavity is narrowed, irregular, or has completely disappeared, the uterine fundus resembling a plain massive muscle (Figs. 3 and 4). (3) Cervico-isthmic synechiae are often but not always associated with hematometra and sometimes hematosalpinx. The development of these lesions depends upon the functional state of the remaining endometrium.



Fig. 3.



Fig. 4.

Fig. 3.—Uterine cavity almost obliterated by synechiae.

Fig. 4.—Corporeal synechiae which led to complete obliteration of uterine cavity.

Clinical Study.—We shall first describe the most common and characteristic type, the corporeal synechiae.

Hypomenorrhea is the most common complaint. The menstrual periods remain regular. Menstruation may consist only of a slight brownish discharge. Hypomenorrhea may be replaced by amenorrhea. Amenorrhea often precedes hypomenorrhea and lasts a few months after which it disappears spontaneously or after endocrine therapy. When hypomenorrhea occurs, however, it does not respond to any endocrine therapy.

The onset of hypomenorrhea and of amenorrhea after a dilatation and curettage is an important phenomenon, the importance of which should be stressed. It is obviously of primary clinical importance. In our series, the dilatation and curettage was performed only once for a gynecological non-obstetrical disorder. The development of menstrual insufficiency followed dilatation and curettage after abortion in 28 of our cases. It often develops following a postpartum curettage. We feel that curettage is very seldom indicated post partum, the softening of the uterine tissue being most probably responsible for the inevitable abrasion of the uterine muscle. Uterine synechiae may also develop after simple uterine packing. Sometimes there is no menstrual disorder when the synechiae occupy a comparatively small surface, and the diagnosis is made in the course of hystero-graphy performed for sterility or repeated abortions.

Pelvic examination shows no palpable abnormality. Obstruction of the external os of the cervix makes diagnosis easy; otherwise it is necessary to attempt to pass a calibrated sound through the cervical canal into the uterus. Sometimes the instrument is stopped very abruptly by an obstruction, generally at the level of the isthmus or slightly lower.

These clinical findings can be a guide to the correct diagnosis, when one has already seen similar cases. Also, the absence of any signs of ovarian insufficiency may aid in the diagnosis; it is to be pointed out, however, that there are some exceptions as shown in our second case and 6 others of the 42 studied. These 7 patients had some symptoms of the menopausal type.

Diagnosis.—Diagnosis is based essentially on hystero-graphy which must be performed with a short cannula. Occasionally the cannula cannot be introduced without previous dilatation of the external os of the cervix, or perhaps of the whole cervical canal; during such dilatation of a partially or totally obliterated cervical canal, obviously great caution must be exercised.

Typical synechiae are easily recognizable at the first glance from their characteristic lacunar pattern, alone or multiple, of variable size, centrally or peripherally located. They are characterized also by their irregularity, their angulated and very clear-cut contours, their homogeneous opacity, and their presence on every film (Figs. 5-8).

Cervico-isthmic synechiae are easily diagnosed by hystero-metry. As previously mentioned, sometimes the cervical os has disappeared or it is the size of a pinhole opening, as, for example, in the menopausal patient or following cauterization. These, as with post-curettage adhesions, may lead to the development of hematometra. Hystero-graphy in these cases is usually impossible without previous cervical dilatation under general anesthesia. It may, however, be necessary because it aids in the differentiation of the cervico-isthmic from the isthmio-corporeal synechiae.

Evolution.—When synechiae have formed, they are permanent. They are hardly to be considered a disease. Many women, when informed of the cause of their disorders, prefer to remain as they are rather than have an operation. Hematometra is painful and may produce adnexal complications. It calls for

surgical treatment. If by chance pregnancy occurs, abortion and premature delivery are more likely to occur, as well as low insertion of the placenta. Delivery of the placenta is difficult and dangerous on account of abnormal placental adhesions.

Pathogenesis.—Hald⁶ examined microscopically curettings from 4 patients who developed intrauterine synechiae. He found uterine muscle in each instance. Synechiae are nothing else than a scar secondary to the healing of a wound. The theory of Asherman^{2, 3, 4} that a permanent contraction of uterine muscular fibers occurs which narrows the isthmus and results in adhesion of the opposite surfaces is without any sound basis.

Fig. 5.

Fig. 6.

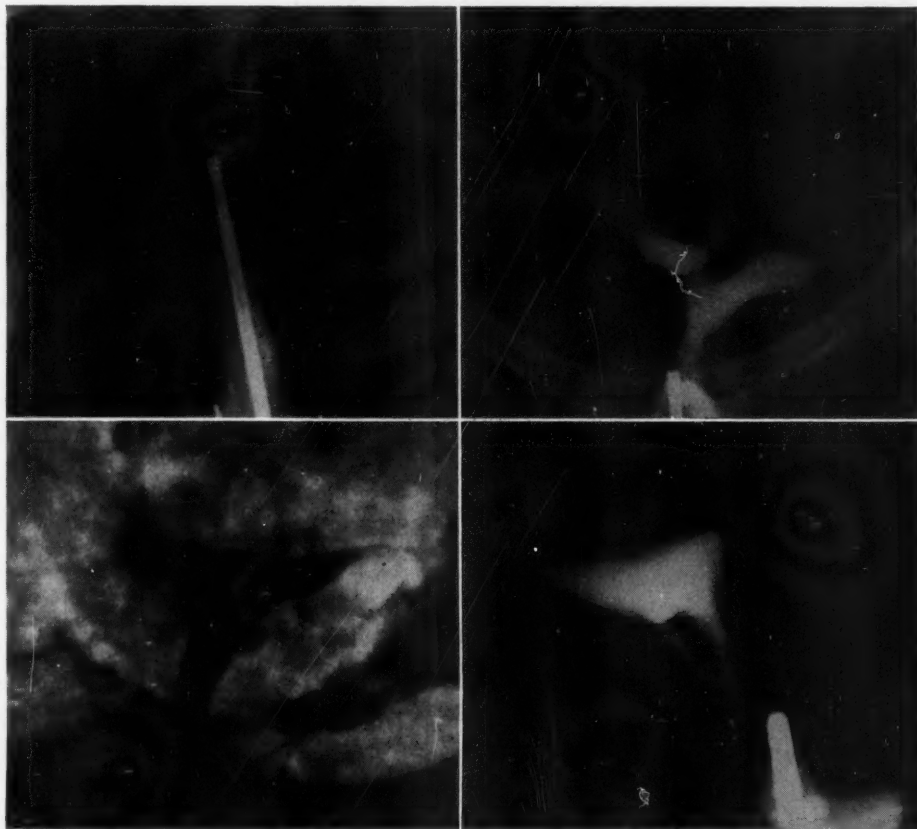


Fig. 7.

Fig. 8.

Fig. 5.—Attempted hystero-gram showing evidence of extensive synechiae.

Fig. 6.—Synechiae of fundus.

Fig. 7.—Central corporeal synechia.

Fig. 8.—Isthmic and supraisthmic synechiae.

Physiopathology.—The physiopathology of menstrual insufficiency is quite obvious too. Asherman believes that menstrual insufficiency is observed only in patients with isthmic adhesions and that corporeal adhesions result only in impaired fertility. Analysis of roentgenograms and of serial sections of

surgically removed uteri leads to the following conclusions: (1) Synechiae of the fundus are the most frequent and lead to hypomenorrhea or amenorrhea. (2) Synechiae of the isthmus result either in simple hypomenorrhea or hematometra, the physiopathology of which is obvious. Four out of five of our patients who had cervico-isthmic adhesions had hematometra. In the fifth case blood was probably escaping into the peritoneum through the tubes.

Treatment.—Treatment is almost always surgical.

1. Cervico-isthmic synechiae can be treated by the vaginal approach.

The cervical canal is dilated or reconstituted and its patency is maintained by a metallic tube which is left in situ for five or six days. If there is hematometra, antibiotic therapy is indicated. Hematosalpinx compels one to perform a laparotomy. Generally, conservative surgery is possible—salpingostomy and re-establishment of cervical patency as well as conservation of the uterus and the ovaries.

2. The treatment of corporeal adhesions is not so easy to define.

Nonsurgical treatment is occasionally possible. For example, if the diagnosis is made during delivery, the adhesions may be broken up with the fingers or occasionally with scissors. In a nonpregnant patient adhesions less than one year old may also very occasionally be treated by dilatation and digital uterine maneuvers. In all other cases, nonsurgical treatment must be rejected not only because of its inefficiency but also because of the danger and likelihood of perforation of the uterus during treatment.

Old adhesions must be treated through the abdominal approach or through the combined abdominal vaginal approach. After abdominal hysterotomy the synechiae are freed digitally, or more often with the aid of scissors. The cervix is then dilated and a metallic drain is left inside the cervix. A metallic catheter previously introduced into the corpus uteri through the cervix greatly aids in the identification of the uterine cavity; that is why we recommend the technique that uses two surgical teams.

Summary and Conclusions

Curettage, especially during the postpartum or postabortal period, results not infrequently in adhesions of the uterine wall, adhesions which can cause in extreme cases complete disappearance of the uterine, cervical, and isthmic cavities.

These adhesions are responsible for a very large number of the cases of hypomenorrhea. The clinical picture in these cases is characteristic enough to suspect the cause; hysteroscopy shows their existence; and hystero-graphy makes the diagnosis certain, at the same time giving us precise information as to the extent and anatomical type of the adhesions.

Applying this method of investigation to patients with menstrual insufficiency, we were helped in ascertaining the frequency of cases of synechiae not suspected before.

The endocrinologist must take this diagnosis into consideration and can no longer ignore this lesion.

Medical treatment of this type of menstrual insufficiency is completely unsuccessful. The only treatment for the cases causing serious genital troubles is surgical as outlined in this paper.

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LIPOMAS OF GYNECOLOGIC INTEREST*

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A LIPOMA consists of normal fat usually arranged in irregular lobules separated by fibrous septa. It may or may not be demarcated by a connective tissue capsule. It is one of the most innocent of tumors but may on occasion become malignant.¹ Lipomas may be of a pure or mixed type, e.g., fibrolipoma.

While lipomas are common tumors and are frequently encountered in the neck, shoulders, back, and buttocks, they are also noted in such unusual sites as the kidney, mesentery, bowel, and central nervous system. They are uncommon in the female genital tract. The fact that, with the exception of the labia majora, the female organs do not possess any fatty tissue accounts for the scarcity of these tumors. Thus case reports have illustrated their presence in the labia, vagina, uterus, oviducts, ovaries, and in the supportive elements, e.g., broad ligament, round ligament, etc. We have not been able to locate a lipoma of the uterosacral ligaments.

These lipomas are of interest not only because of their scarcity but because they vary markedly in size, shape, and consistency. They may interfere mechanically with the function of surrounding organs, and on occasion may become malignant and lethal. This is particularly true of the retroperitoneal types.

Etiology

The etiology of lipomas of the female genital tract is indeed a moot question. As previously mentioned there is no fatty tissue in the genitals save in the labia majora. The theories are many, and an understanding of the development of the reproductive tract is imperative. A simple outline of the embryology is as follows: "The tubes, uterus, and vagina develop from the Müllerian duct which originates during the second week from a thickening of the celomic epithelium. The duct begins as an elongated invagination in the urogenital ridge. Its folds then fuse and canalize to form a tube. Fusion followed by canalization proceeds cephalad to caudad. The inner ends of the two ducts meet to form the uterus, whereas the upper parts remain free to form the tubes. The uterus and vagina form from the fused inferior parts of the ducts."²

The gonad develops in that part of the genital ridge where the mesonephros is located. The first phase consists of an accumulation of dense cellular mesenchyme into primary cords. These primary cords fuse with secondary cords

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produced by the surface epithelium. As a result of further not clearly understood embryogenesis, the ovary with its tunica, germinal epithelium, and stroma then completes the cycle.

Merkle³ quotes Virchow as differentiating lipomas into two general types: (a) *hyperplastic*: those found in locations where fatty tissue is usually found, e.g., the labia majora; (b) *heteroplastic*: those found in locations where fatty tissue is not usually found, e.g., uterus, cervix, ovary, etc. Some types are difficult to differentiate. The formation of the heteroplastic types was attributed to two etiological factors: (1) metaplasia and proliferation of connective tissue cells into fatty tissue cells; and (2) misplaced embryologic (lipoblastic) rests of fatty tissue.

Merkle shared Virchow's opinions. Wells and Adair⁴ believe that the earliest adipose tissue is derived from primitive connective-tissue elements. This adipose tissue may develop into two types: (1) highly differentiated true fat tissue, as a result of ingrowth of fat tissue along vessels or nerves from neighboring structures; (2) ordinary connective tissue without embryonic differentiation, which takes on intracellular fat as an adventitious property because of local or general conditions. Further consideration should be based upon study of the possible origin of lipomas with regard to specific genital structures.

The Uterus.—Knox⁵ considered lipomatous tumors of the uterus as supporting Cohnheim's embryonic-cell-rest theory, e.g., that embryonic fat cells left behind during development later produced tumors. Seydel⁶ regarded them as originating from lipoblastic dislocations because he could not demonstrate the formation of fat cells from either muscle or connective tissue. Brunnings⁷ suggested the possibility of muscle cells changing into fat cells. von Franque⁸ attributed the development of fat cells to the infiltration of connective tissue by fat globules. Starry,⁹ after meticulous microscopic study of his specimen, revealed the presence of developing fat cells in the connective tissue. He concluded that these fat cells develop from connective tissue (the reverse of von Franque's idea), probably representing a special differential type of (lipogenic) connective-tissue cell.

We have, then, two prime schools of thought: (1) *theory of metaplasia*, stressed by Brunnings, von Franque, and others, and (2) *theory of dysembryoplasia*, advocated by Seydel, Starry, and others. These speculations were promulgated with the intention of explaining the origin of pure lipomas. How is it possible, then, to account for the presence of mixed lipomatous tumors, e.g., fibrolipomas? Burger¹⁰ rationalized as follows: When the Müllerian ducts invaginate in the Wolffian eminence, they are able to carry mesodermal tissue from the subperitoneal layer. This mesodermal layer contains germinal tissue capable of forming muscle, connective, or fatty tissue. Thus there may arise a single or mixed type of fatty tumor.

The Oviducts.—Modifications of the aforementioned theories have been used to explain the existence of oviductal lipomas. Parona,¹¹ in describing the first case recorded in the literature (1891), stated that lipomas could develop and grow from tubal and ovarian tissue. He felt that the tumor probably started to grow at the fimbria and then diffused into the oviduct and ovary. Samperno¹² believed their origin to be by metaplasia from reticulomesenchymal tissue. Pape¹³ thought that they originated from embryonal rests. This theory is shared by Herrmann¹⁴ who wrote that these misplaced clusters of fat cells

are inert but may be stimulated to tumor formation by some stimulus such as pregnancy, inflammation, etc. Bogetti,^{11a} after meticulous microscopic studies of his case, indicated that lipomas of the oviduct originate at the sites where the blood supply is the greatest, e.g., the mesosalpinx. Shaw¹⁵ and Samperno are in accord. Shaw believed it possible for a lipoma to arise from the subperitoneal tissues of the Fallopian tubes since it is not uncommon to find fat cells in this region.

The Ovary.—Fatty tissue is not usually seen in the ovary, not even in obese women. Von Szathmary¹⁶ stated that, in this case, the lipoma of the ovary was secondary to the appendices epiploicae, by way of adhesions. Herrmann^{14a} listed four possible sources for the presence of lipomas of the ovary: (1) lipoblastic rests which persist from the ligamentum latum or ligamentum ovarii proprium; (2) rete ovarii; (3) teratoma of the ovary with its multipotentialities; and (4) connective-tissue stromal metaplasia.

Broad Ligament and Pelvic Connective Tissue.—The majority of intraligamentous lipomas are secondary to retroperitoneal growths, though primary types can occur.^{17, 18} Doran¹⁹ suggested some teratologic element. Stagg and Hunter²⁰ felt that metaplasia from connective tissue is a possible etiologic factor. Greensfelder and Bettmann²¹ stated that retroperitoneal tumors usually arise from paranephritic fat, but may also arise from the renal capsule, the mesentery, the pararectal and retrorectal fat. Retroperitoneal lipomas occur with about equal frequency on either side of the pelvis or abdomen.

The Round Ligament.—Curtis²² has written that lipomas of the round ligament may arise from the ligament itself, since fatty elements are normal to the round ligament; from the paraligamentous fatty tissue, excluding the labia majora; or from embryonic remnants.

Vulva and Clitoris.—Lipomas of the labia majora may arise from fatty tissue normal to the labia, or from the round ligament which inserts therein. The possibility of metaplasia of connective tissue and the presence of embryonic lipoblastic remnants applies to both the labia and the clitoris.

The Clinical Picture

Lipomas of the Uterus.—Henriksen,²³ reviewed the literature and brought the total number of "true lipomas" of the uterus to 24. Since then 2 cases have been reported by Dontenwill²⁴ and Kovats.²⁵ To this number we wish to add one in a patient of our own, making a total of 27 cases thus far reported.

None of the tumors have been diagnosed preoperatively. The usual mistaken diagnosis made prior to operation is fibromyomas of the uterus. On one occasion the preoperative diagnosis was appendiceal abscess, rule out gallstones. A review of the history in that 71-year-old patient justified the preoperative impression.²⁶

These lipomas occur in women who are usually in the fifth to the seventh decade of life. The youngest thus far reported in the literature was 39 years of age.²⁷ The complaints made by the patients have been typical of fibromyomas of the uterus, e.g., swelling of the abdomen, deep pelvic pressure or pain, menstrual dysfunction, postmenopausal bleeding, frequency, urgency, and backaches. Nausea, vomiting, constipation, and shortness of breath were lesser complaints occasionally noted. On the other hand, there may be no complaints whatsoever, and the tumor noted coincidentally as a result of operation for some other condition. The patient is usually afebrile on admission, unless some secondary complicating factors exist. Some have indicated that the abdomen may be large enough to suggest a term pregnancy.

The tumor will vary in size from a few millimeters to quite a few centimeters in length, width, breadth, and depth.

Grossly, those of the corpus resemble lipomas found anywhere in the body, though a prevalence for the fundus is noted. They are usually readily differentiated from uterine tissue by a pseudofibrous capsule. In an occasional case, unstriated muscle fibers have extended into the tumor. The contour is as a rule spherical. The tumors vary in location and may be noted on the serosa, muscle, or actually extending into the uterine cavity as polyps. Further, those which extend outward may easily make their way into the broad ligament. Lipomas may exist in the presence of some other uterine neoplasm such as a fibromyoma, sarcoma, or carcinoma.

Cervical lipomas may resemble a typical polyp or appear as an intramural cervical tumor, e.g., a fibroma. They were the first of the uterine lipomas to be described. Although but 6 cases of cervical lipomas have been reported in the literature, we feel that more have been seen and not publicized. Malignant degeneration of uterine lipomas is a real danger. Six such cases have been noted in the world literature.²⁸⁻³³

Lipomas of the Oviduct.—In 1935 Bogetti³⁴ stated that there have been described but 6 cases of lipoma of the salpinx. Three of them were true lipomas, one was a fibrolipoma, one was a lipolymphangioma, and one an adenomyolipoma. The first case of true lipoma of the oviduct was described by Parona³⁵ in 1891. The last case to be recorded was the seventh reported in world literature (Bogetti). This patient was a 38-year-old housewife who complained of discomfort in the right inguinoabdominal region, and of tightness in the lumbar region of the back. Physical examination failed to disclose any noteworthy findings. Because of persistent complaints, a laparotomy was decided upon. A lipoma about the size of a walnut was found on the anterior aspect of the left oviduct. It was yellow in color, firm to palpation, sessile in character, and encapsulated. The treatment was salpingectomy.

Bleeding may be a complaint, in addition to pain. In 1928, Shaw¹⁵ described a 40-year-old married, sterile housewife, who complained of irregular bleeding of two years' duration. Examination showed the surface of the uterus to be somewhat irregular, and a cystic mass measuring about 2 inches was palpated in the region of the left adnexa. Surgically the tumor was found to arise from the anterior surface of the isthmic portion of the oviduct. On section, a small collection of tarry fluid escaped. The tubal mucosa and the lipoma were distinct and separate. Pape³⁶ described a fibrolipoma the size of a date on the oviduct of a 32-year-old woman who had an ectopic pregnancy on the contralateral side. This patient had no previous complaints.

In summary, these tumors may be symptomatic or asymptomatic. Two such lipomas were found during the course of an autopsy. The symptom most likely to occur is discomfort, with or without bleeding. These patients have all been in the childbearing age. The size may vary from a few millimeters to the size of a date, or a walnut. The involved oviduct may contain only the lipoma or some associated pathologic finding such as a lymphangioma. All have been discrete, surrounded by a pseudocapsule, and easily separated. None were diagnosed before the abdomen and pelvis were exposed.

Lipomas of the Ovary.—These are exceedingly rare. We have been able to find but 3 cases in the literature. von Szathmary¹⁶ stated that in his patient the lipoma was secondary to the appendices epiploicae by way of adhesions. Herrmann^{14a} found a lipoma on the right ovary 1 cm. in diameter, nodular, yellow, and encapsulated. The opposite ovary was in good condition. This 37-year-old woman had died of septicemia following injury to a large toe. There had been no abdominal or pelvic complaints.

In 1941 Fahr³⁷ reported an unusual fatty tumor of the ovary. The patient had complained of deep pelvic pain. The indication for operation was a fixed

retroflexed uterus. Both adnexa and uterus were found adherent to the parietal peritoneum. The appendix was also adherent with diffuse fine adhesions. The right ovary showed a small nodular elevation on its inferior surface. Microscopically, this consisted of large and small atypical fat cells, and minimal interstitial vascular elements. Fahr also stated that a similar case had been previously reported by Madlener.

Lipomas of the Broad Ligament and Pelvic Connective Tissue.—Up to the present time only 20 cases of broad ligament lipomas have been reported in the literature. The first case in this series was reported by Pollack in 1852 (quoted by Stagg and Hunter²⁰). The most recent case was that presented by Funck-Brentano.³⁸ Forgue and Crouse¹⁷ stated that the principal characteristics of these tumors of the broad ligament are: (1) their tendency to assume considerable volume; (2) their indolence, and (3) their progressive growth. Most complaints are due to the mechanical effects of pressure on the surrounding structures. They may be unilateral or bilateral. They may be large enough to suggest the possibility of a pregnancy. Rawls³⁹ reported one case wherein the tumor weighed 33 pounds. Middleschulte (quoted by Stagg and Hunter²⁰) removed one that weighed 33 pounds and measured 88 by 90 cm.

The age of these patients has varied from 31 to 70 years. The symptomatology has varied according to the size of the tumor, its location, and the secondary manifestations of the viscera imposed upon. In several instances the tumors have presented in the perineal region. Flickinger and Masson⁴⁰ have stated that if a patient has a reducible tumor in or near the perineal region, the possibility of a lipoma must be kept in mind. If this mass can be felt to enter the pelvis gliding alongside the vaginal canal, one must consider the possibility of a lipoma of the broad ligament extending beyond the confines of the pelvis or an obturator hernia. Murray⁴¹ reported such a case in a woman of 25, who complained of swelling in the abdomen and pressure about the vagina. There was nothing abnormal in the abdomen. The right buttock on the inner side of the gluteus maximus presented a localized prominence about 2 inches in diameter. Vaginal examination showed this mass to be continuous with an elongated swelling on the right side of the vagina. The vagina was narrowed by the growth. At operation a pelvic lipoma was found extending downward behind the pubic arch toward the thigh.

The most common mistaken preoperative diagnoses have been: (a) ovarian cyst; (b) parovarian cyst; (c) tuberculous salpingitis and peritonitis; and (d) chronic pelvic inflammatory disease. In a review of the literature Lang and Bland⁴² found the following associated pathologic conditions: (a) dermoid cysts (3 patients), (b) fibromyomas of the uterus (1 patient), (c) chronic adnexitis (1 patient), (d) adenocarcinoma of the corpus (2 patients), (e) severe hydroureter (1 patient).

Retroperitoneal lipomas are most likely to occur in women who are 50 years of age and over. The symptoms are usually vague, varied, and associated with minimal pain. Swelling of the abdomen is the most constant complaint. They occur equally on either side of the abdomen or pelvis. These tumors may be pure or mixed. Lockyer⁴³ draws a sharp distinction between "pre-vertebral" lipomas and those of the broad ligament and omentum. He described the former as adherent, difficult to remove, having a tendency to undergo sarcomatous degeneration, and associated with a heavy mortality. The latter were described as more often benign, nonadherent, easily removed, with a good prognosis.

Submucous lipomas of both the large and small bowel are not unusual. In a comprehensive study of lipomas of the large bowel, Cavanaugh⁴⁴ found that 152 cases have thus far been reported in the literature. These patients are

usually in the cancer age, the average age being 52 years. The most common complaints noted are pain, constipation, diarrhea, blood (gross or microscopic) in the stool, weight loss, nausea, vomiting, and anorexia. Obviously the preoperative diagnosis is usually carcinoma.

Lipomas of the Round Ligaments.—These may be intraperitoneal or extraperitoneal, depending on whether they are inside or outside the inguinal ring. Accordingly, the mass may be in the groin or labia, or deep in the pelvis, or in both locations. The tumor may be unilateral or bilateral. The size and shape are variable. Ducuing⁴⁵ reported the case of a 5-year-old girl who had a small tumor of the left groin at birth. The tumor developed slowly. At 3 months the tumor occurred on the opposite side. At 5 years these tumors had grown to a size which required their removal. In 1946, Flickinger and Masson⁴⁰ reported the intrapelvic types of round-ligament lipomas; one on the right side and one on the left side. To these we wish to add one of our own, making a total of 4 as reported in the literature.

Lipomas of the Vulva and Clitoris.—Lipomas of the external female genitals are more common than those of the internal genitals. The presence of fatty tissue in this area, excluding the clitoris, would tend to explain this prevalence. Salaber and Nogues⁴⁶ indicated that in 1903 Kelly had collected 20 cases of lipomas of the external female genitals from the world literature. In 1923, Lovelace⁴⁷ reviewed 45 such cases, and in addition reported the largest lipoma of the labia majora ever noted before or since. Salaber and Nogues were able to collect another 20 cases from 1923 to 1941, making a total of 65 cases reported in the present literature. We wish to add 2 of our own, making a total of at least 67 thus far reported.

The presenting complaint is that of a mass in the groin or labium, usually associated with pain. The tumor varies in size from that of a pea, to that of a grapefruit. Broutzel^{46a} reported a case in which the lipoma extended into the vagina and obstructed the birth passage of a patient in labor. The tumor may extend alongside the round ligament into the inguinal canal, thereby resembling an inguinal hernia. The growth is slow and usually progressive. Differential diagnosis of lipomas in this area includes a consideration of: (a) inguinal hernia, (b) lymphogranuloma or granuloma inguinale, (c) metastatic invasion of the inguinal lymph glands, (d) tuberculous adenitis, (e) hidradenoma, (f) cyst of the Bartholin gland, (g) solid tumors of the labia, such as fibromas, and (h) cystic tumors of the round ligaments.

We have been able to find but one case report on lipomas of the clitoris.⁴⁸ A 6-year-old girl was referred to the clinic as a pseudohermaphrodite. Examination showed a tumor of the prepuce. The tumor seemed well delineated. There had been no complaints, so that the duration was unknown. Differential diagnosis in this patient included: fibroma of the clitoris and hypertrophy of the clitoris. Excision of the tumor was easily performed, and the microscopic study showed it to be a pure lipoma.

Case Reports

Lipoma of the Uterus.—Mrs. M. J., a white woman, aged 70, entered the Presbyterian Hospital complaining of pressure sensation in the vagina for many weeks, and of painful urination. Examination showed the uterus to be enlarged to the size of a 3½ to 4 months' gestation, symmetrical and smooth. Clinical impression was that of fibromyomas of the uterus. A total hysterectomy and bilateral salpingo-oophorectomy were done. The uterus contained a single intramural mass, the size of an orange. The tumor was yellow in color, doughy on palpation, and lobulated. The pathology report indicated it to be a lipoma, wherein the adipose tissue was dispersed with fibrous septa. It stained well with sudan III.

Lipoma of the Labia Majora (2).—Mrs. P. E. B., aged 55, menopausal for 7 years, complaining of a mass protruding from the vagina for 6 to 8 months, loss of urine when coughing or straining, and mild prolapsus of the rectum. A mass the size of an egg was palpated in the left labium majus. It was surgically removed without any difficulty. Pathologically it was reported as a lipoma with fibrous septa.

Mrs. G. Y., aged 29, gravida ii, para ii, complained of a mass the size of a baseball, hanging from a pedicle, attached to the left labium. The tumor was easily excised, consisted of soft fatty tissue, pearly white in color, and weighed 270 grams. Histologically it proved to be fat tissue.

Lipoma of the Broad Ligament (2).—Miss E. G., aged 47, gravida i, para 0, complained of a dull, localized pain in the right lower quadrant for the past 6 months. For the past 24 hours she had felt a sharp pain in the right lower quadrant which caused her to double up. Her menstrual history was not noteworthy. The mass was palpated in the pelvis and on the right side. Operation disclosed an old hemorrhage into the right ovary, and a mass the size of an orange in the right broad ligament. Grossly the broad ligament tumor was a lipoma. The microscopic report verified this impression.

Mrs. L. G., aged 37, gravida iv, para iv, started her menstrual period with discomfort, followed by more bleeding than usual, and with the passage of clots. Examination showed a retroverted uterus deviated to the right by a moderately soft ovoid mass in the left adnexal area. At operation a mass was found, golden yellow in color, the size of a grapefruit, and located in the left broad ligament. The mass was easily enucleated and with little loss of blood. Grossly the tumor was lobulated, and appeared to be a lipoma. Microscopically it was "fat tissue" which stained with sudan III.

Lipoma of Broad Ligament Extending Paravaginally.—Mrs. M. S., aged 34, gravida iv, para i, had a cesarean section performed six months previously because of a paravaginal mass obstructing labor. It was difficult to do a bimanual examination on the patient because of a soft cystic mass which obstructed the introitus. Clinically the diagnosis made was a cyst of Gartner's duct. No fluid could be aspirated. The operation was done vaginally. A mass the size of a grapefruit was separated from the adjacent tissue and broad ligament. It was surrounded by a pseudocapsule, weighed 370 grams, and appeared to be of fatty composition. A sulfonamide-saturated pack was inserted in the surgical wound, and was gradually removed within the next 96 hours. Histologically the mass consisted of bright yellow fat, with fibrous tissue septa.

Lipoma of the Round Ligament.—Mrs. E. S., aged 31, gravida v, complained of primary sterility for the past 3½ years, dyspareunia, and deep right-sided pain in the lower abdomen. Examination showed a fibromyoma of the uterus, the size of a 5 months' pregnancy. At operation the right round ligament contained a mass 9 cm. in length and 35 mm. in diameter. On section it was a homogeneous, pale yellow, fatty tumor, weighing 45 grams. Only occasional fibrous septa were noted. A subtotal hysterectomy and appendectomy were also performed.

Retroperitoneal Lipoma.—Mrs. A. H., aged 57, gravida ii, para ii, who had gone through the menopause 10 years before, complained of pain in the right lower quadrant. At operation 51 grams of encapsulated homogeneous tissue was removed from the right lateral retroperitoneal area of the pelvis. Histologically there was marked chronic inflammation along the periphery of the tumor.

Lipoma of the Cecum Extending Into the Pelvis.—Miss L. C., a single, 18-year-old white woman, complained of right lower abdominal pain for 1½ years. These attacks were recurrent and accompanied by nausea. Rectoabdominal examination showed a fairly good-sized mass which was diagnosed as an ovarian cyst. At operation a mass extending from the cecum into the pelvis was found. The tumor was easily removed, measured 19 by 15 by 7 cm. and grossly appeared to be a lipoma. Microscopically the tissue was fat, and infiltrated by thin fibrous septa.

Summary and Conclusions

1. Although lipomas of the female genitals are uncommon, they have been reported as occurring in every structure of the genitals other than in the uterosacral ligaments. These tumors are of gynecologic import because they can interfere mechanically with the function of surrounding organs, and on occasion may become malignant.

2. The etiology and pathogenesis of pelvic lipomas are herewith reviewed.

3. Twenty-six cases of pure lipoma of the uterus are now recorded in the literature. None of these tumors have been diagnosed preoperatively. The usual mistaken diagnosis is fibromyomas of the uterus. These lipomas have occurred in women who are usually in the menopausal or postmenopausal stage of life.

4. Six cases of malignant degeneration of uterine lipomas have thus far been reported.

5. Pain, with or without bleeding, is the outstanding complaint caused by lipomas of the oviduct. Bogetti, after a thorough perusal of the medical annals, was able to find only 6 cases. These patients have all been in the child-bearing age.

6. Lipomas of the ovary are exceedingly rare. We have been able to find only 3 cases in the literature.

7. Lipomas of the broad ligament are characterized by the following traits: (a) their indolence, (b) their tendency to assume considerable volume, and (c) their progressive growth. The most common mistaken preoperative diagnoses have been: (a) ovarian cyst, (b) parovarian cyst, (c) chronic salpingo-oophoritis.

8. Lipomas of the broad ligament may extend into the perineal area. These tumors can extend downward alongside the vaginal canal and partially or completely occlude the passage.

9. Retroperitoneal lipomas are characterized by abdominal swelling, and are associated with minimal pain. Lockyer has subdivided these tumors clinically into the potentially malignant prevertebral types, and into the usually benign broad-ligament and omental types.

10. Lipomas of the round ligament may be intra- or extraperitoneal, depending on whether they are inside or outside the inguinal ring.

11. Lipomas of the external genitals are more common than those of the internal genitals. At least 67 cases of lipomas of the labia have thus far been recorded in the literature. The presenting complaint is that of a mass in the groin or labia, usually associated with pain.

12. A complete differential diagnosis of lipomas of the external genitals will include a consideration of ten different possible causes.

13. Only one case of lipoma of the clitoris has been reported. The case summary is herewith presented.

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Discussion

DR. GEORGE H. GARDNER.—Hearty congratulations to Dr. Kanter and to Dr. Zummo, first, on their comprehensive review of lipomas of the female generative tract; next, on their unusually extensive clinical experience with such tumors, as well as the large number of new cases which they have added to those already recorded in the literature. They have told us about lipomas in the labia, the vagina, the cervix and corpus of the uterus, the uterine tubes, and the ovaries, as well as in the round and broad ligaments; but all of these are so rare that they have precious little clinical importance; they are primarily of pathologic interest.

My own limited experience justifies the following few comments:

1. Several patients have reported, in recent years, because of tumors which they thought arose from the genitals, but which, in reality, were lipomas of the upper thigh. With me, such a location has been more frequent than the vulva.

2. I recall an instance of 3 small subserosal lipomas of a uterine tube; these were chance findings in a patient with uterine myomas.

3. Our studies of those commonly encountered broad-ligament cysts of mesonephric and paramesonephric origin have made us aware of the striking infrequency with which true neoplasms arise there; from those recorded in the literature, it appears that lipomas are the most frequent solid tumors arising from normal structures of the broad ligaments.

4. During his residency with us, Dr. Larry Gossack chanced upon multiple submucosal lipomas of the ileum, while operating for the "residues" of a previous pelvic infection. One of these tumors was of sufficient size to cause low-grade bowel obstruction, with moderate distention of proximal loops of small intestine.

5. About four years ago I operated on an obese Negro multipara of 45 for uterine fibroids that made a mass about the size of a 3½ months' gestation; the indications for operation were profuse menses with moderate anemia, and chronic pelvic pain. When opened, this symmetrically enlarged uterus contained a single tumor, about 9 cm. in diameter, which arose from the posterior wall of the corpus and bulged into the uterine cavity. On section, it was a discrete tumor and appeared to be degenerated, with a mottled cut surface—in part yellowish and in part pale gray, and softened.

Microscopically, it was composed of lobules of fat cells with intervening broad septa of fibrous tissue and bundles of smooth muscle fibers. It was considered to be a leiomyolipoma, and benign.

Such tumors are not to be confused with fatty degeneration in a leiomyoma; in fact, this is an extremely uncommon type of degeneration, even in this garden variety of uterine tumor which is so prone to undergo various other types of degeneration. Obviously it is not a true lipoma. By some it probably would be termed a "mixed" tumor, and as such would be considered much more likely to eventuate in sarcoma, than would be true for a pure lipoma of the uterus.

It seems most probable that lipomatous uterine tumors arise from mesenchymal cells, normally present in the uterus; hence no one should be surprised if we look askance at any explanation of their histogenesis which presupposes displaced embryonic lipoblasts.

SOME FURTHER OBSERVATIONS ON WIDE SKIN UNDERCUTTING FOR INTRACTABLE PRURITUS VULVAE

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PRURITUS vulvae often becomes intractable and debilitating when it fails to respond to the commonly used therapeutic measures and techniques. In September, 1952, a group of 16 cases were reported¹ in which wide undercutting of the skin of the vulva, perineum, suprapubic, perirectal, thigh, and inguinal areas was used. The operation was devised to replace mutilating vulvectomy which had always been considered as a last resort in these exceptional cases. The first operation was performed in February, 1947, and at this writing the operation has been performed 57 times in cases which had resisted all other therapy for periods of two years or longer. Of the original 16 patients, approximately 95 per cent remained asymptomatic for one or more years. The results were so encouraging that further trial was felt to be justified.

The extremely wide undercutting of the vulvar skin has two main objectives, namely, severance of most of the nerve supply to the area and an increase in vascularity of this region. Experience shows that the desire to scratch is lost and the vascularity improves as a result of almost complete neurectomy and neurosympathectomy. Inflammatory changes, such as edema, fissures, pin-point or gross ulcerations, seem to subside completely, the skin returning to normal in most instances. Extensive leukoplakia and malignancy must be ruled out prior to operation. The photographs, technical description, and method of applying the Elastoplast dressing are included in the original publication.

One discussion of this method of correction has recently appeared in the literature, with report of a case, using the same technique. Burger² at the University Frauenklinik in Wurzburg, Germany, feels that the method can be used not only for intractable symptomatic pruritus vulvae, but also for leukoplakia and kraurosis, provided malignant change has been ruled out by biopsy. He discussed the advantages of breaking the "vicious cycle" by severing sensory nerves supplying this area, and the increased vascularity which results in restoration of traumatized skin to a normal healthy state.

The following figures are based on the first 55 cases, all followed over one year. The remaining 2 cases have been observed less than one year and are not included. Seventeen have been lost to follow-up after one year. It is assumed that these women after relief for so long a period would have returned in event of recurrence. There were 2 complete failures in which a vulvectomy was subsequently done, and 3 partial recurrences statistically considered as complete failures. One very interesting development was shown by the 3 partial recurrences. The area of recurrent pruritus was localized to a small segment of

skin in all 3 and was excised under local anesthesia with disappearance of symptoms. Thus, with a minor secondary operation, these 3 women have again become asymptomatic and were spared mutilation from excision of large sections of skin. Table I merely shows what has been accomplished in this series and is not intended as an analytical review of the problem.

TABLE I

Total number of cases over one year	55	100%
Complete failures	2	3.7%
Partial failures	3	5.5%
Successful correction of symptoms (Includes 17 cases lost to follow-up after first year)	50	90.8%

Careful selection of cases is imperative or such a procedure could easily fall into quick disrepute. Most elective operations are frequently resorted to with inadequate preliminary investigation. None of this group were considered candidates for surgical trial until the following criteria had been considered:

1. Practically continuous pruritus for two or more years.
2. Cultures and smears negative for fungi or parasites.
3. Metabolic diseases ruled out.
4. Common allergens eliminated if possible.
5. Failure of other forms of therapy to produce lasting cure.
6. Inability to rest or sleep.
7. Physical and mental impairment.
8. Suicidal tendencies.
9. No evidence of extensive leukoplakia or suggestion of malignant change.

Wide undercutting of the vulvar area is reasonably simple to perform. The skin can be separated easily from muscle, fascia, vaginal mucosa, and around the anus by the use of two 8 to 10 cm. incisions through the major labial skin at its external margin and carried down to the fascia leaving the subcutaneous fat attached. A thin strip of skin can be taken from each incision for microscopic study. The skin over the groin, pubic area, thigh, perineum, and anal region is easily separated except for nerves and vessels in the pudendal area where the major difficulty is encountered. Careful dissection is necessary in the perineal and anal regions so as not to injure the rectum. Aside from these areas, the operation proceeds rapidly and undercutting for a radius of 8 to 12 cm. in all directions can be performed without danger, hemorrhage, or other difficulty. Good hemostasis is important. The subcutaneous layer is drained with a single Penrose drain brought through the fascia above the clitoris and out of the lower angle of each incision. The fat layer is closed over the drain by single interrupted sutures of fine catgut and the skin approximated with fine silk mattress sutures. A Foley catheter is inserted in the bladder and a Zephiran gauze pack in the vagina. An Elastoplast pressure dressing from posterior to anterior costal margin over fluffed gauze prevents collection of fluid in dead space, controls oozing, and promotes primary healing.

It is interesting to note that accompanying rectal pruritus also responds well, probably because this skin area is denervated at the same time. In the past, when this type of operation was used, and subsequently discarded by

proctologists, the chances are it failed because the small area of undercutting did not sever the large nerves, especially those of the pudendal area.

The initial postoperative period of approximately eight weeks is most critical to success. These patients must be re-educated and we think should be taught new habits of dress and hygiene. They are asked to follow very carefully the following list of instructions which is presented them on discharge from the hospital:

1. Under no circumstances is the skin of the affected area to be scratched.
2. Do not wear clothing which comes in contact with the vulva and thighs.
Example: no panty girdle; the ordinary girdle is permitted.
3. Do not wash area with any kind of soap or detergent. Use nothing but plain water on a clean washrag, and the parts should be sponged off with clean water after voiding and defecation and dried thoroughly using soft clean cotton material.
4. Douche twice weekly with plain lukewarm water.
5. Take a moderately hot sitz bath daily for 15 minutes until instructed otherwise.
6. If menstrual periods still occur, use tampons only. Under no circumstances use external sanitary napkins.
7. No medication of any kind permitted near the area. This is to include all ointments, salves, or other forms of external applications.
8. These instructions are subject to change after the initial eight weeks of the postoperative healing period.

Early pruritus is mostly reversible if properly diagnosed and treated. Long-standing pruritus with continuous scratching can bring about a distinct disease entity of badly damaged or often destroyed areas of skin. Beginning with the first operation performed in 1947, all of the 57 undercutting operations were done on women with pruritus vulvae of two or more years' duration. They were all intensively investigated and treated for years by nonsurgical means until skin changes with some destruction were grossly evident. The simpler approaches to the problem consistently failed to alleviate their symptoms. Indeed, the use of any surgical method to alleviate a symptom should await the repeated failure of simpler, less drastic, and very often effective trial of nonsurgical therapy. This includes alcohol injections; procaine pudendal block; elimination of fungi and parasites; thorough study of metabolic, allergic, and psychic factors; the use of local emollients, etc. Surgical methods except for biopsy are not necessary; but if vascular and neurogenic changes occur, local, x-ray, and other forms of therapy become valueless, forcing one to resort to more drastic treatment. Preliminary local therapy for years if necessary and even psychotherapy are recommended prior to surgery.

Long discussions with many patients point to the fact that the psychic factor with development of the habit of scratching even while sleeping is probably the most difficult to combat. The undercutting operation may be the only means by which the habit can be broken; either by severing the nerve pathways, or simply by the magnitude and psychic shock of operation, or both. Occasionally one sees large trophic ulcers which are evidence of more severe trauma and are seen in some very long-standing cases. X-ray dermatitis has been rather commonplace in this series and follows a history of repeated exposures to x-ray with

thickening of the cutis, loss of hair, and changes in pigmentation. In an occasional case, there will be no gross evidence of trauma. This poses a problem from the psychic angle, especially in a strong-willed individual who avoids scratching, but still insists she is symptomatic. Willingness to undergo this operation after careful explanation of its scope would indicate need for some form of assistance.

Biopsies of skin obtained at operation have shown only a low-grade inflammatory process in the subepithelial layer in the large majority of these women. None showed microscopic changes neoplastic in nature. There were 3 cases that could be classified as early leukoplakia. The latter were of great interest from a clinical standpoint. Six months after operation they could no longer be classed as such from gross appearance. No second biopsies have been secured to show absence of rete pegs and metaplasia of the basal-cell layer, but the lesion subsided grossly, suggesting possible return to normal. These 3 cases will be followed closely for recurrence of gross change in the appearance of the skin. If such gross changes occur, a strip of skin will be obtained for section and pathological examination. Could it be possible that early leukoplakia is reversible? This concept is projected for study on those with early, fairly localized lesions. Strips of affected skin will be taken pre- and postoperatively with careful follow-up in all future cases of suspected leukoplakia.

In most cases there has been considerable edema of the operative sites after removal of the pressure dressing; this subsides quickly and may be completely disregarded. No other unusual postoperative complications not included in the original report have been noted.

Some features of this operation are very quickly apparent:

1. Immediate, spectacular relief from pruritus.
2. Nonmutilating procedure.
3. Nons shocking procedure. (Minimal blood loss. No transfusions necessary.)
4. Increased circulation.
5. Rectal area not touched in vulvectomy included.
6. Practically all nerve pathways disrupted.
7. Healing per primam.
8. Ease of performance.
9. Elimination of intractable pruritus with constant trauma may prevent malignant change in the vulvar skin.
10. Marked change for the better in quality and texture of skin indicating the value of breaking the "vicious cycle."

Oversimplification of the problem of pruritus is to be condemned and avoided. It is a symptom of a complicated array of dermatological entities, vexing and confusing and difficult to treat, often very lightly regarded by specialist and general practitioner alike. The one fact stands out: if allowed to persist for long periods, it can result in severely traumatized areas, the main symptom being marked pruritus. We are concerned with the case of badly damaged skin because further scratching adds insult to injury. Thus despite any form of treatment occasional insoluble problems of this kind will occur and they confront the practitioner of medicine with a challenge. With all due

respect to the opinion, publications, and good results obtained by dermatologists, allergists, roentgenologists, and gynecologists who eventually treat most of these cases, there apparently will always be some patients who continue to be symptomatic.

It should be emphasized that no effective nonsurgical possibility which will correct pruritus should be lightly regarded. This operation is not intended to supplant other methods, but only to provide a possible way to avoid mutilation of the area which cannot be avoided if large areas of skin are sacrificed. Vulvectomy has not always solved the problem and is particularly debilitating to young women with long life expectancy. Vulvectomy should be employed only for extensive leukoplakia or malignant growth, proved by biopsy. The gynecologist as a "court of last resort" must decide what method or operation will give the patient the best chance for cure. This operation seems to offer an excellent chance of success as attested by the 90.8 per cent correction factor of one year or longer.

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MONILIA (CANDIDA) ALBICANS: A CULTURE AND ELECTRONIC pH STUDY

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ALKALINE douches and medications continue to be advocated and taught as the proper treatment of vaginal infection due to *Monilia (Candida) albicans*, largely in the belief that, in vitro, the fungus grows best on highly acid culture medium and, in vivo, in the highly acid vagina of the pregnant woman. Interest in and investigation of this problem have indicated that these teachings need to be re-evaluated, and the following study was undertaken.

Culture Study

The first step was to study the growth of *Monilia (Candida) albicans* on Sabouraud's culture medium prepared to pH range of 3.90, 5.64, 6.19, 6.54, 7.42, and 10.82 by the addition of increasing amounts of 0.01 normal sodium hydroxide solution.

The results of this study were indeed interesting. Table I shows that *C. albicans* is able to grow at both a very acid and a highly alkaline pH range. Fig. 1 illustrates the growth of the fungus at different pH levels, and Fig. 2 shows photomicrographs of the fungus taken from a culture at a pH of 6.65. Three things are evident: (1) *C. albicans* appeared the same under the microscope at any pH examined; (2) when the culture medium became dry, only the yeast (conidial) form of the fungus was present, and (3) when the medium was fresh and damp, the branching (mycelial) form predominated.

TABLE I. GROWTH OF MONILIA (CANDIDA) ALBICANS ON SABOURAUD'S CULTURE MEDIUM AT VARYING pH RANGE

NO. OF TUBES USED	NO. OF PETRI DISHES	pH OF MEDIUM	GROWTH
12	0	3.90	All 4 plus
24	5	5.65	All 4 plus
5	6	6.54	All 4 plus
8	6	7.42	All 4 plus
31	4	10.82	All 4 plus
Total	80	21	

Electronic pH Study

The second step in the study was to obtain electronic pH readings* of vaginas infected with *Monilia albicans*. The pH was determined of the four vaginal walls—right, left, anterior, and posterior—from the fornix to the hymenal ring. The tips of the electrodes were slowly moved along the vaginal walls. Recordings on normal vaginas were used as a control group (Fig. 3). Then recordings were made of the four vaginal walls in 30 patients with vaginal moniliasis.

*A Minneapolis-Honeywell Electronic pH Recorder was used.

The pH of the leukorrhea was recorded as this secretion lay in the posterior blade of the speculum, and it was of interest to note that more acid was constantly produced in this leukorrhea as it came in contact with air. This

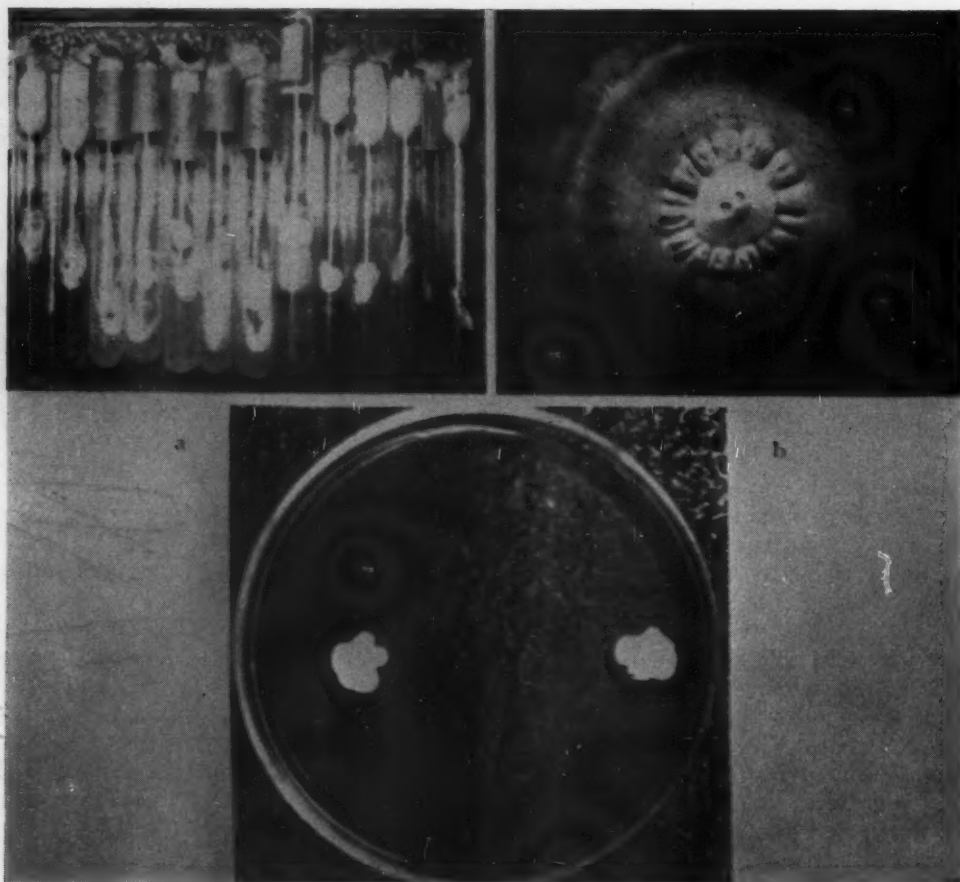


Fig. 1.—Upper left, Sabouraud's slants from pH 3.90 to 10.82 with *Monilia albicans* growth. Upper right, Large solitary *Monilia albicans* growth at pH 5.00. Lower center, Petri dish containing two 4-day-old *Monilia albicans* cultures; the right half of the dish has a pH of 5.64, the left half a pH of 8.11. The two cultures are almost identical.

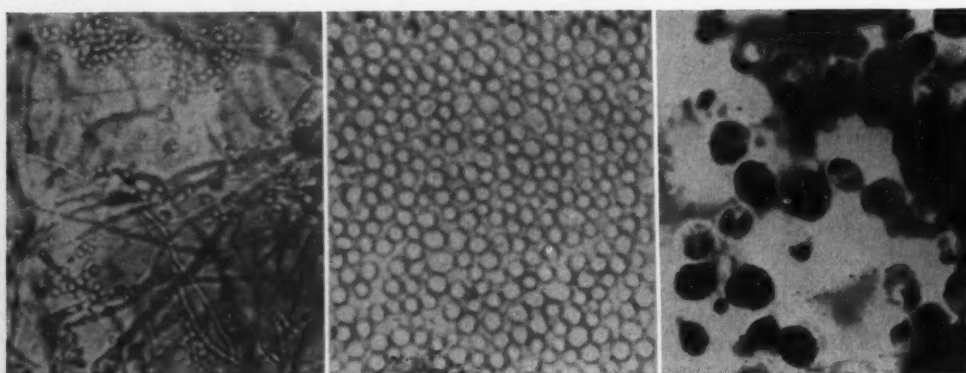


Fig. 2.—Left, Photomicrograph of *Monilia albicans* showing mycelial (branching) and yeast (spore) stages. Center, Yeast stage unstained. Right, Stained yeast stage.

suggests that the glycogen in the freshly collected leukorrhea breaks down into more lactic acid than that present in the original leukorrhea which is in a somewhat anaerobic state on the vaginal wall. In more severely infected vaginas, the leukorrhea did not exhibit this phenomenon of becoming more acidic. The pH usually remained approximately that of the vaginal walls or moved toward the alkaline side.

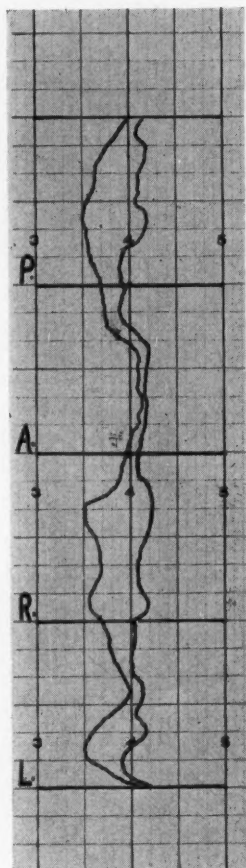


Fig. 3.—Electronic pH recordings of normal vaginal walls. The normal vaginal pH varies from 3.50 to 4.20.

The pH in the majority of cases of vaginal moniliasis fell between 5.00 and 6.50, although it was noted that there was marked variation from one vaginal wall to another and even in different areas of the same wall.

The results of this phase of the study can best be presented by detailed interpretation of Figs. 4, 5, 6, and 7. In these illustrations, all recordings are read from the bottom up; *A* represents the anterior vaginal wall from the fornix to the introitus; *P* the posterior vaginal wall; *R* and *L* the right and left lateral walls, and *LE* the leukorrheal pH recorded as the secretion lay in the posterior blade of the speculum.

Fig. 4 presents electronic recordings in six cases (Cases 1-6) of vaginal moniliasis in which the pH varied from 3.99 to 6.05. As more pathology developed in the vaginal epithelium, the more nearly the pH approached a level of 7.00 to 8.50.

Fig. 5 presents the electronic pH recordings on two more patients (Cases 7, 8) (Case 7 is approximately 75 days pregnant) with vaginal moniliasis in whom the pH ranged from 5.80 to 6.92, the range in which the majority of cases of vaginal moniliasis fell. The letter *U* indicates the red, irregular lesions so often seen in vaginal moniliasis which begin to form on the vaginal walls at a pH of 5.80 or above. White flakes also begin to form on the vaginal walls at the same pH (5.80).

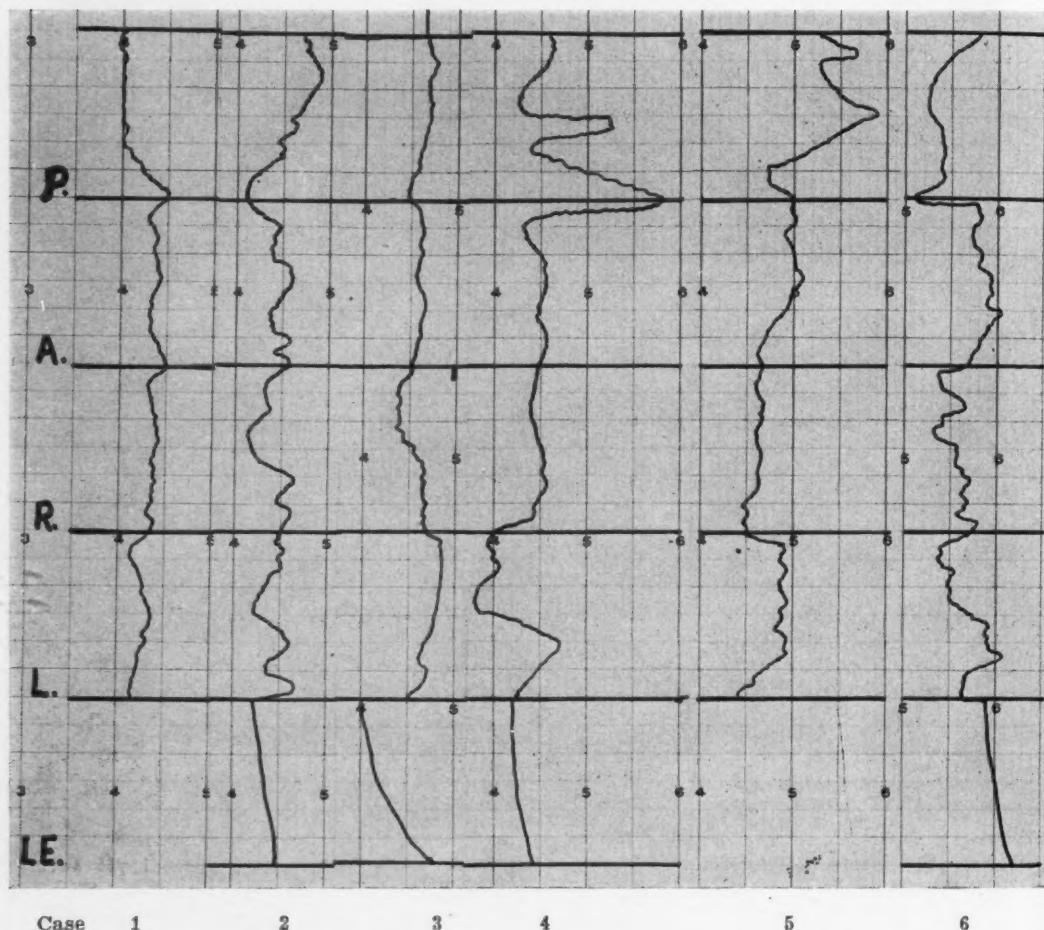


Fig. 4.—Six electronic readings of six different cases of vaginal moniliasis in which the pH varied from 3.99 to 6.05.

Fig. 6 presents the electronic pH recordings of three patients (Cases 9-11) with a more severe type of moniliasis with the pH varying from 6.00 to 7.92. In Case 9, the pH varied from 6.00 to 6.80, only yeast (conidial) forms of the *Monilia* were found, and the vagina was very sore. Case 10 shows the marked differences in pH that may be recorded in cases of vaginal moniliasis. The vaginal secretion in this instance was dry, white, and crumbly. Case 11 shows the pH recording in a case of acute vaginal moniliasis in which the entire vaginal wall was covered with the typical white, irregularly shaped flakes or curdlike, cheesy material in a nonpregnant patient who was menstruating regularly.

Fig. 7 shows six different grades (I through VI) of pH recordings found in vaginal moniliasis. The pH range in chronic monilial vaginitis is 5.00 to 6.00; in subacute, 6.20 to 6.70; in ulcerative, 7.50 to 8.50, and in acute, 6.70 to 7.78. All acute vaginitis, regardless of the cause, had the same pH, as shown in Grade V of this figure. Seldom was *C. albicans* found near a pH of 4.00 and in the few cases occurring near this pH, signs and symptoms were rarely produced. Since the majority of *Monilia* infections were found between 5.00 and 6.50, it is obvious that there is a hypoacid state in most vaginal moniliasis.

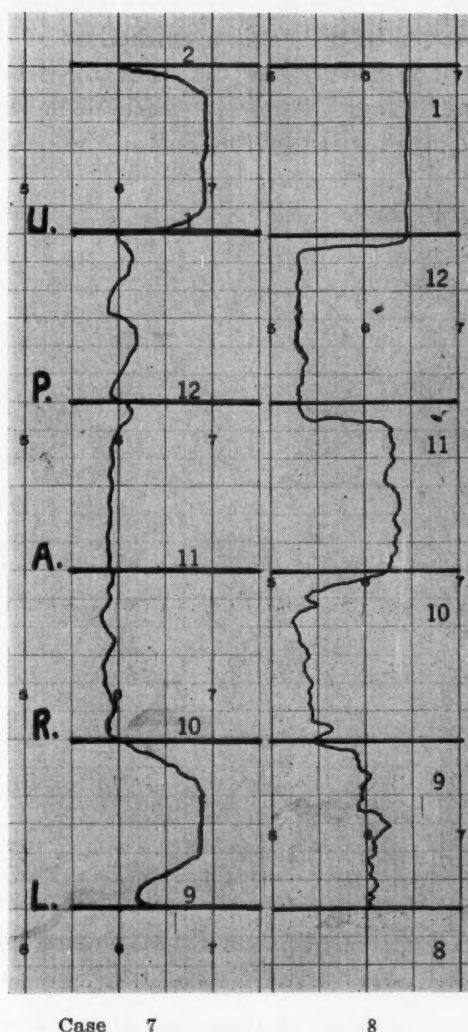


Fig. 5.—Electronic pH recordings in two cases of vaginal moniliasis. The letter U indicates red, irregular lesions so often seen in moniliasis.

Comment

Monilia (Candida) albicans, frequently found in the vagina of the pregnant woman, is apparently nurtured by the constant low pH (highly acid) vagina common in such patients, yet in most cases this is not as acid as the normal vagina during pregnancy, which has a pH range of 3.50 to 4.20.

Although the pH of the normal vagina in pregnancy and in nonpregnancy is the same, greater amounts of acid or acids are produced in the vaginal epithelium of the pregnant woman. The increased amounts of lactic and possibly other organic acids in the vagina of a pregnant woman kill many of the associated microorganisms but do not always destroy *C. albicans*. Decreased competition due to the absence or inhibition of other vaginal microorganisms favors the growth as well as the possibility of survival of *C. albicans*. A second factor favoring the growth of this fungus is the more constant production and increased storage of glycogen in the vaginal epithelium of the pregnant woman, on which *Monilia* is able to survive. A further factor, I believe, is a deficiency of vitamin B complex, vitamin C, and the trace elements in the vaginal epithelium due to increased utilization by the mother and baby.

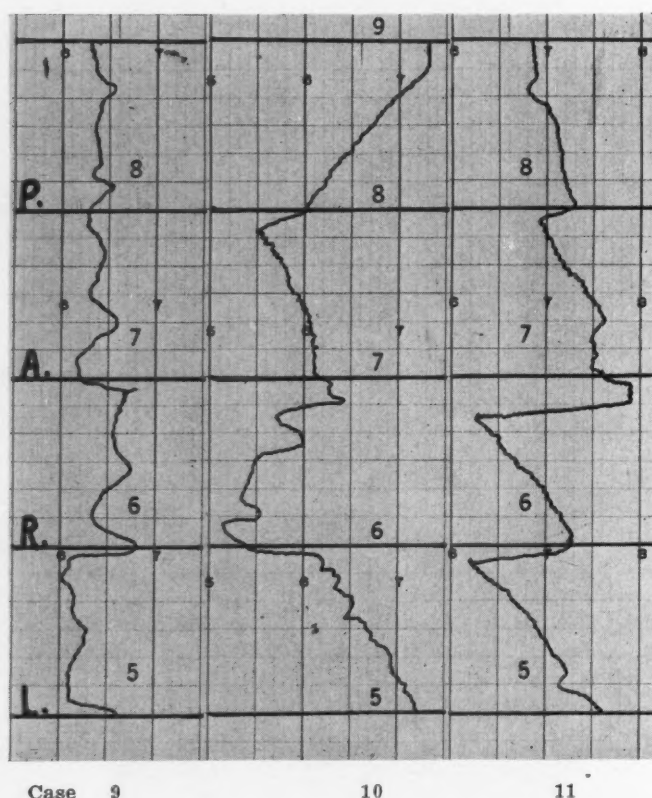


Fig. 6.—Electronic pH recordings of three cases of severe vaginal monilliasis.

There are apparently other factors in the vaginal epithelium and secretion of the pregnant woman that kill or inhibit the growth of most of the associated vaginal microorganisms, such as the constant presence of large and increasing amounts of both estrogen and progesterone, the absence of the menstrual fluid with its highly buffered alkaline serum and blood, and the presence of *C. albicans* which may itself give off a secretion that destroys other vaginal microorganisms,

In pursuing these studies on the effect of alkaline and acid medications on leukorrhea, I have observed both grossly and microscopically that most alkaline preparations cause a mushy coagulation of vaginal secretions containing *C. albicans*, *Trichomonas*, and other organisms. When these coagulated vaginal secretions were incubated or kept at room temperature, there developed a prolific growth of many kinds of vaginal microorganisms which produced a very foul odor. On the other hand, if the vaginal secretions were mixed with a correctly buffered, correctly acidified medication containing an adequate amount of spreading agent and then incubated, *C. albicans* was killed; there was either no or very poor growth of vaginal pathogens, yet there was growth of the normal vaginal microorganisms, such as Döderlein's bacilli, without production of offensive odors. It was repeatedly noted that acid medications tended to liquefy vaginal secretions.

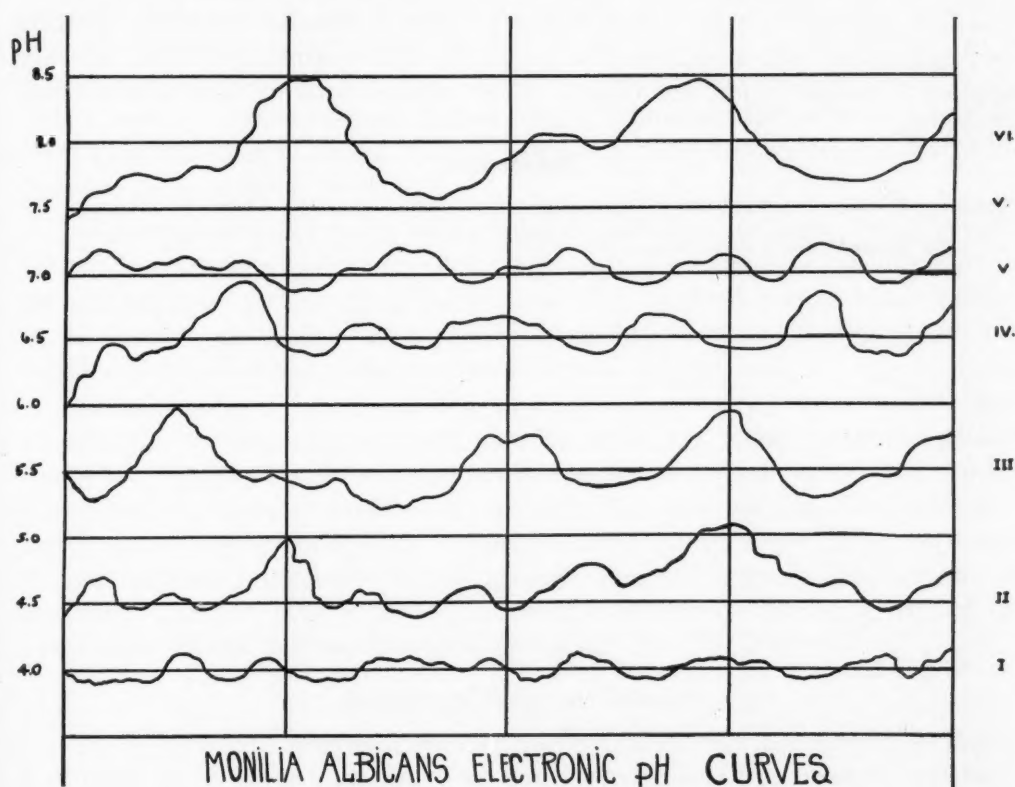


Fig. 7.—Grades I through VI of electronic pH recordings found in vaginal moniliasis infections in the Leucorrhea Clinic.

Conclusions

1. Pathogenic *Monilia (Candida) albicans* cultures are identical grossly and microscopically when grown on Sabouraud's culture medium within a pH range of 3.90 to 10.82.
2. Electronic pH recordings in this series of patients with vaginal moniliasis ranged from 3.99 to 7.91.

3. From these studies it might be assumed that *C. albicans* will grow at almost any pH found in the vagina with the exception of the lower part of the normal pH range, namely 3.50 to 3.79; *C. albicans* has not been found in this low-acid pH range.

4. Alkaline medications are not recommended in the treatment of vaginal moniliasis because, due to the *Monilia* infection, there is already present a hypoacidity of the vagina. Most vaginal moniliasis occurs at a pH range of 5.00 to 6.00, which demonstrates that there is marked loss of normal acidity of the vagina in vaginal moniliasis. Therefore, the administration of alkaline medications or douches adds more injury to an already pathologic vaginal epithelium.

5. Alkaline medications cause vaginal secretions to coagulate, forming a favorable medium for growth of pathogenic vaginal microorganisms.

6. Correctly acidified and buffered spreading agents, douches, ointments,* powders, and tablets† have been found to destroy *Monilia (Candida) albicans* and pathogenic microorganisms when mixed with vaginal secretions or when applied to the perineum and vagina. Such preparations are nontoxic and non-allergenic.

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*Poborin ointment: potassium aluminum sulfate 2 grains and sodium lauryl sulfate 2 grains in 20 per cent boric acid and lanolin, 2 ounces; can be obtained only in 2 ounce tube.

†Baculin powder and tablets contain:

Potassium alum 14 mg.
Lactose 430 mg.
Sodium lauryl sulfate 3 mg.
Di-iodi-8-hydroxy-quinoline 100 mg.
Phenylmercuric acetate 3 mg.
Dextrose anhydrous 430 mg.
Papain 20 mg.
Cornstarch and kaolin as filler.

TREATMENT OF URINARY TRACT INFECTIONS IN OBSTETRIC AND GYNECOLOGIC PATIENTS WITH NITROFURANTOIN*

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FURADANTIN (brand of nitrofurantoin N.N.R.) is a relatively new chemotherapeutic molecule designed specifically for the treatment of bacterial infections of the urinary tract. The drug is indicated in pyelitis, pyelonephritis, and cystitis where severe renal damage is not present. Bacteria sensitive to Furadantin include such refractory species as *Escherichia coli*, *Proteus*, *Pseudomonas*, and *Aerobacter* species. Following oral administration, approximately 40 per cent of the drug is excreted in the urine. Its solubility in urine obviates the danger of crystalluria.

Of eleven clinical reports on Furadantin published to date, none mentions its use in pregnancy. Because of the relatively high frequency of infection of the urinary tract among pregnant women, we report our results in such cases. These patients were observed closely to ascertain whether there might be any possible toxic effects on either mother or fetus.

In this study, 33 women with pyelonephritis or cystitis were treated with Furadantin. Eleven of these patients were pregnant. In one pregnant patient the infection was chronic and had not responded to several antibiotics. In the nonpregnant group, 11 cases were chronic. The average dose was between 5 and 8 mg. per kilogram of body weight per twenty-four hours, taken by mouth in four divided doses daily, following meals and at bedtime. The duration of treatment varied between four and twenty-one days. The majority of the cases were treated for seven successive days.

Results in Pregnant Women

In 10 of the 11 pregnant women, the diagnosis was acute pyelonephritis, 3 of these cases being bilateral. One patient had acute hemorrhagic cystitis.

Urinalyses and urine cultures were performed on all patients before treatment was initiated and were repeated after seven days of therapy. In 5 patients, urine cultures were made twenty-eight days after the beginning of therapy.

The over-all evaluation of the results was determined by both the clinical improvement and satisfactory laboratory results, namely, the absence of pus cells in the urine and negative bacterial cultures.

*This investigation was supported in part by a grant from Eaton Laboratories, Norwich, N. Y.

All of the 11 pregnant patients with acute infections who were treated became entirely asymptomatic in seven days or less and 9 had negative urine cultures after seven days' treatment.

The only untoward effect observed was nausea or vomiting which occurred in 5 cases. In only one patient was this side reaction of such severity that the drug had to be discontinued after four days' therapy. Headache did occur in a few cases but was not thought to be caused by the drug since this complaint usually disappeared along with the other symptoms of infection while the patient was under treatment.

One patient aborted a fourteen-week fetus one day after therapy was initiated but she had had a diagnosis of threatened abortion three days prior to the beginning of therapy. There were no other findings in other patients suggesting that pregnancy was a contraindication to Furadantin therapy.

Results in Nonpregnant Women

The diagnosis and results in the 22 nonpregnant patients are shown in Table I.

TABLE I

DIAGNOSIS	ORGANISM	RESULTS	CULTURE
<i>Pregnant Patients.</i> —			
Acute hemorrhagic cystitis (1)	<i>E. coli</i>	Asymptomatic	7 days positive (1)
Acute pyelitis (10)	Gram-positive rod (2)	Asymptomatic (2)	Negative (2)
	<i>A. aerogenes</i> (3)	Asymptomatic (2)	Negative (2)
		Improved (1)	Positive, <i>E. coli</i> (1)
	<i>E. coli</i> (5)	Asymptomatic (5)	Negative (5)
	<i>S. albus</i> (2)	Asymptomatic (1)	Negative (1)
		Improved (1)	Positive, <i>E. coli</i> (1)
<i>Nonpregnant Patients.</i> —			
Chronic pyelonephritis (9)	<i>P. vulgaris</i> (1)	Asymptomatic (1)	Negative (1)
	<i>E. coli</i> (6)	Asymptomatic (3)	
		Improved (2)	Positive culture (4)
		No improvement (1)	Negative culture (2)
	Beta hemolytic strep. (2)	Improved (1)	Positive culture (1)
	No improvement (1)	Negative culture (1)	
Acute cystitis (6)	<i>E. coli</i> (6)	Asymptomatic (5)	Negative (4)
		No improvement (1)	Positive (2)
Acute pyelonephritis (4)	<i>E. coli</i> (2)	Asymptomatic (2)	Positive (1)
			Negative (1)
	<i>P. vulgaris</i> (1)	Asymptomatic (1)	Negative
	<i>A. aerogenes</i> (1)	Asymptomatic (1)	Positive,
			<i>A. aerogenes</i> (1)
	Hemolytic <i>Staph. albus</i> (1)	Asymptomatic (1)	Negative (1)
Chronic cystitis (3)	<i>E. coli</i> (2)	No change (1)	Negative (2)
		Asymptomatic (1)	Positive (0)
	<i>P. vulgaris</i> (1)	Asymptomatic (1)	Negative (1)

Summary and Conclusions

Furadantin was used to treat acute and chronic urinary tract infections in 11 pregnant and 22 nonpregnant women. Successful results were obtained in all pregnant patients and in all but 3 of the nonpregnant.

This preliminary investigation indicates that Furadantin is an effective drug and that pregnancy is not a contraindication to its use.

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DETECTION OF INVASIVE CERVICAL CANCER BY EXFOLIATIVE CYTOLOGY

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THERE is general agreement at present that it is feasible to detect carcinoma of the cervix by means of exfoliative cytology within limits of accuracy entirely acceptable for clinical practice. Routine screening examination of vaginal smears for cervical carcinoma is now considered by many physicians an essential part of the complete physical examination of all female patients in the fourth decade or later.

At present a substantial percentage of the cervical lesions now being detected by cytologic examination consists of so-called "carcinoma in situ," "preinvasive carcinoma," or "noninfiltrative carcinoma." There has developed accordingly an intense interest in the relationship between carcinoma in situ and invasive cervical carcinoma. Indeed, it has been asserted by McDonald¹ recently in a symposium on cytology that "... the future of exfoliative cytology in the study of cervical lesions is more or less dependent on whether in-situ carcinoma of the cervix is determined to be a progressive or regressive lesion."

It was felt that studies directed at the exact nature of the lesion being currently detected by cytologic screening might shed light on this fundamental question. The material following has been accumulated with this end in view, and is composed of data on 4,200 patients seen in a clinic-type practice.* These were all examined with vaginal smears as a screening procedure. No attempt at selection on any basis has been made.

In this study 18 cases in which a histologic diagnosis of carcinoma was ultimately made are recorded in Table I. In each of these cases the initial clinical impression was other than carcinoma, the first positive indication of malignancy being the result of cytologic examination. Three cases of clinically evident carcinoma with positive smears have been excluded from this study as immaterial. The physician making the initial smear in each case provided the data listed in answer to a questionnaire which included the following:

1. In what clinic were the smears taken?
2. Did the patient have a specific gynecologic complaint? (If yes, specify briefly.)
3. Was there a visible lesion of the cervix at the time the smears were taken? (If so, give clinical impression.)
4. Was there a biopsy taken at the time of smears? (If so, what was the histologic diagnosis?)
5. List any subsequent histologic diagnosis.

*Permission of the Permanente Foundation Clinic to report these data is gratefully acknowledged.

Of the final histologic diagnoses of cancer made, 10 of 18 proved to be early invasive carcinoma in the opinion of two independent pathologists. Extension into the necks of the endocervical glands was not considered to be true invasion in this study. Eight of these 10 patients were seen in the gynecology clinic by a qualified physician. Six (Nos. 1, 10, 11, 13, 16, and 18) had complaints commonly associated with cervical carcinoma. Three of the 10 had no clinical lesion of the cervix, while 7 lesions were described variously as "cervicitis" or "cervical erosion." In 8 of the 10 cases no biopsy was performed at the time the initial positive smear was made. In 2 of the 8, the cervix was actually by-passed in favor of endometrial biopsy.

TABLE I

PATIENT	AGE	CLINIC	COMPLAINT	CLINICAL IMPRESSION OF CERVIX AT TIME OF SMEAR	BIOPSY AT TIME OF INITIAL SMEAR	FINAL HISTOLOGIC DIAGNOSIS
1. B. J.	65	Gyn.	Spotting	Normal	None	Invasive carcinoma
2. J. B.	44	Gyn.	Irregular periods	Normal	(Endometrial biopsy)	Carcinoma in situ
3. I. W.		Gyn.	Not given	Chronic cervicitis	Chronic cervicitis	Carcinoma in situ
4. D. A.	45	Gyn.	Not given	Chronic cervicitis	Invasive carcinoma	Invasive carcinoma
5. H. B.	36	Gyn.	Pelvic pain	Hypertrophic cervicitis	None	Carcinoma in situ
6. A. S.	43	Gyn.	"Menopause"	Normal	None	Invasive carcinoma
7. L. P.	51	Gyn.	"Vulvar itch"	Cervical erosion	None	Carcinoma in situ
8. A. P.	31	Gyn.	Vaginal discharge	Cervical erosion	Cervicitis	Carcinoma in situ
9. S. O.	38	Gyn.	None	Normal	None	Carcinoma in situ
10. V. N.	36	Gyn.	Metrorrhagia	Cervical erosion	None	Invasive carcinoma
11. L. M.	46	Med.	Metrorrhagia	Cervical erosion	None	Invasive carcinoma
12. D. K.	33	Med.	None	Chronic cervicitis	Cervicitis	Invasive carcinoma
13. R. K.	32	Gyn.	Dyspareunia	Bullous cervicitis	Carcinoma in situ	Invasive carcinoma
14. F. H.	38	Med.	None	Chronic cervicitis	None	Carcinoma in situ
15. M. H.	63	Med.	None	Normal	None	Invasive carcinoma
16. L. H.	33	Gyn.	Menorrhagia	Cervicitis	(Endometrial biopsy)	Invasive carcinoma
17. D. G.	41	Med.	Vaginal discharge	Normal	None	Carcinoma in situ
18. A. F.	43	Gyn.	Menorrhagia	Cervicitis	(Endometrial biopsy)	Invasive carcinoma

In discussion of this latter datum with the physicians involved, the question arose as to whether in a large proportion of these 8 cases no biopsy was performed because the clinician relied on cytologic accuracy. It was agreed that this factor did not operate; in fact, the practice in this service has always been to perform cervical biopsies very freely, if at all indicated, regardless of the availability of the cytologic service.

Comment

Dunn² has represented schematically the pathogenesis of cervical cancer in which a preinvasive stage is present in the following useful manner:

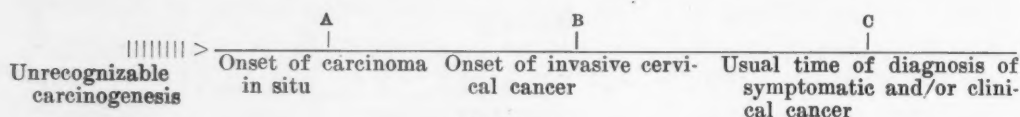


DIAGRAM 1

Let us use a similar scheme for the cervical cancer in which it is assumed that no preinvasive stage takes place.

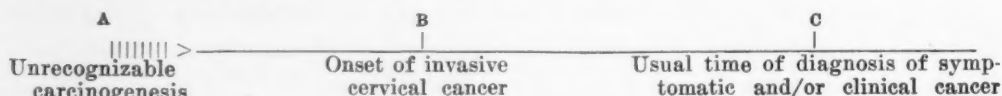


DIAGRAM 2

We may now consider the cytologic contribution to the over-all problem of cervical cancer in these 4,200 individuals in terms of two figures, of which one is known and the other is a percentage of a known.

The first figure consists of 10 cases of invasive carcinoma which may be designated as those prevailing in the interval between B and C in either Diagram 1 or 2. The second consists of "X" percentage of 8 cases which may prevail in either the interval between A and C in Diagram 1 or B and C in Diagram 2. The reason for inclusion of both B-C intervals in the second group arises from the fact that most observers agree that a certain portion of so-called cases of carcinoma in situ can be shown to be invasive when careful serial sections of the entire cervix are examined.

Knowing that some of the cases in this series designated as in situ are in reality already invasive, and that others will become so, let us consider two possibilities. The first might be that a small percentage (say 25 per cent) of the in situ cases are invasive or destined to become so. The total number of cases of invasive or potentially invasive cancer detected would then be 12, or 0.29 per cent, of all examinations performed. The second possibility might be that a large percentage (say 75 per cent) of the in situ cases are invasive or destined to become so. Then the total number of such cases would be 16, or 0.38 per cent, of all examinations.

The value of cytologic examination in this series revolves therefore around other considerations besides that raised by McDonald. These include the mean duration of the period B-C in Diagrams 1 and 2, the increase in curability in cases recognized here rather than at C, and the comparative value of surgical as opposed to radiation therapy in the group of cases regarded as in situ carcinoma and treated surgically which actually are unrecognized very early invasive lesions. There is some evidence at present to show that surgical treatment of this type of lesion may offer a greater prospect of cure than radiation.⁷

In order to compare the type of lesion detected by cytologic means in private practice as opposed to clinic practice, a review of 1,000 consecutive vaginal cytology examinations performed by the author on privately referred patients was made. Six carcinomas of the cervix were detected, all clinically unsuspected. Of this number, 3 proved to be already invasive. While the number of cases is not large, there is at least a strong suggestion that a comparable percentage of early invasive carcinomas will be detected in private and clinic practice.

To return to the question regarding the nature of carcinoma in situ mentioned at the beginning of this paper, it might be well to summarize present concepts briefly. Dunn² has stated this problem very fully in the form of the following three questions:

A. What percentage, if not all, of carcinomas in situ ultimately become invasive carcinoma?

B. What percentage of invasive carcinomas arise as carcinoma in situ?

C. Assuming that all, or a substantial proportion of, carcinomas in situ become invasive carcinoma, what is the average duration of carcinoma in situ, and how much time variation is there around this mean duration?

He points out that no study based on individual cases of cervical carcinoma can provide information on the second of these questions. Furthermore, direct evidence related to the first and third questions is not abundant because of the long time period involved in individual case follow-up.

Despite this fact, several noteworthy contributions to these questions are already available. No definitive answers to these three questions may be forthcoming for another ten years, but there can be little doubt that the problem will in time yield to the combined efforts now being made.

Carson and Gall³ re-examined 718 cervical biopsies in which a diagnosis of chronic cervicitis or squamous metaplasia had originally been rendered. In 13 of these, changes compatible with the diagnosis of carcinoma in situ were found. Follow-up studies of these individuals showed 5 cases of invasive carcinoma diagnosed shortly after the first biopsy, 3 cases of invasive carcinoma diagnosed after intervals of 2, 5, and 12 years, respectively, one individual free from disease after 10 years, and 4 patients not located. They also described 2 cases of "preinvasive carcinoma" and one of "precancerous metaplasia" treated by total hysterectomy, all followed by recurrent vaginal carcinoma.

Evidence gained by a similar approach has been presented by Galvin, Jones, and Te Linde. Seven hundred forty cases of clinical invasive carcinoma were reviewed to determine whether cervical biopsy had been performed on the individuals some time prior to the diagnosis of invasive carcinoma. Thirteen such cases were found, and in all but one instance the previous biopsy tissue revealed carcinoma in situ.

Hertig and Younge⁵ have assembled the following arguments favoring the thesis that carcinoma in situ is actually true carcinoma in a preinvasive stage:

1. The general prevalence of one lesion is comparable to that of the other, while the mean age of incidence of carcinoma in situ is lower than that of invasive carcinoma.

2. The prevalence of both conditions in Jewish women is almost the same, as compared to the prevalence in non-Jewish women (one to six and one to five, respectively, for preinvasive carcinoma and invasive carcinoma).

3. They cite a number of cases of carcinoma in situ observed to progress from this status to invasion.

4. They observe that increasing degrees of cellular atypism are observed by cytologic methods as the in situ lesion becomes invasive.

5. The pattern of in situ carcinoma is described as nearly always present at the periphery of invasive carcinoma.

6. Both lesions are observed to exhibit identical light-absorption patterns when examined by ultraviolet illumination.

Evidence against the relationship between carcinoma in situ and invasive carcinoma is offered by Kottmeier,⁶ who followed 41 individuals with untreated carcinoma in situ for a ten-year period during which only one patient developed invasive carcinoma.

There is a high incidence of a pattern similar to carcinoma in situ seen in the cervix of pregnant women, which appears to regress spontaneously after delivery. This suggests the possibility of a similar regression in nonpregnant women.

It can be said with assurance at this time only that carcinoma in situ may be followed by invasive carcinoma, but that the frequency and time relations of this sequence of events are undetermined. Regarding the lesion which has become invasive or which is invasive from inception, no disagreement exists that early diagnosis and treatment are of paramount importance and that detection in the so-called "preclinical" state is highly desirable. The foregoing material is offered as evidence that cytologic screening is an important means of achieving this end.

Conclusions

1. Data accumulated from a series of screening examinations for cervical cancer are presented.

2. Evidence is offered that cytologic screening is of distinct value in detection of early invasive carcinoma of the cervix in the preclinical state, as well as in detection of carcinoma in situ, more than half the cases detected in this series being already invasive.

3. A partial summary of the current opinion as to the relationship of in situ carcinoma to invasive cervical carcinoma is presented.

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441 NORTH CAMDEN DRIVE

ACCIDENTALLY ENCOUNTERED CERVICAL CANCER

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IN A previous publication we at the Rhode Island Hospital Tumor Clinic recorded our experience with surgery in the total management of cervical cancer. We evaluated our entire operative series, which represented 251 cases, or 21.4 per cent of 1,168 patients seen in the thirty-year period from 1922-1951. In this study we were interested in the over-all problem, and in particular our own comparative experience. We evaluated these patients from four different viewpoints: (1) those who were operated on without the prior knowledge that cervical cancer existed, (2) those who were operated on for palliation only, (3) those whose operation was of an investigative nature, and (4) finally those cases in which surgery was undertaken definitively for cure of cervical disease.

Table I shows a breakdown of these four surgical types according to the stage of the disease they represent, and it shows as might be expected that the earlier stages are more amenable to surgery, regardless of the type.

TABLE I. BREAKDOWN OF SURGICAL TYPE INTO STAGES

	ACCIDENTAL	PALLIATIVE	INVESTIGATIVE	DEFINITIVE	TOTAL
Stage 0	3	1	0	11	15
Stage I	13	18	7	23	61
Stage II	6	45	16	27	94
Stage III	3	25	12	10	50
Stage IV	2	9	8	0	19
Stage ?	0	4	4	4	12
Total	27	102	47	75	251

Our present study involves a more detailed analysis of our accidental surgical series. We believe this group to be highly significant and important. This will become an increasingly important problem now that total hysterectomy is almost everywhere replacing the subtotal operation. It should increase in frequency in direct proportion to the anticipated decrease in cancer of the cervical stump.

Definition.—By accidental we mean that, prior to operation, which was the universal method of management in this group, no consideration of cervical cancer was entertained. It should here also be borne in mind that the staging of these cases was done retrospectively by members of our Tumor Clinic Staff.

Material.—Twenty-seven of the 251 patients under study, or 11 per cent, fell within this grouping, and Table II depicts some of the statistical material considered. We naturally investigated all of the usual factors, but they did not seem relevant enough to merit report. Six of our cases fell within the first fifteen years of our study, and the remaining 21 occurred from 1937 to 1951.

We believe that the tendency toward complete hysterectomy is reflected here in the last 15 years of this study. A further reference to and the significance of this change will be made later.

TABLE II. STATISTICAL TABLE ACCORDING TO STAGES FROM 1922 TO 1951

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
No. cases	3	13	6	3	2	27
Age	43	41	46	45	30	40
Service	33%	69%	50%	67%	100%	63% Priv.
Parous	33%	77%	67%	100%	100%	71% Pos.

One of the main things brought out by this table is that about two-thirds of the cases were the responsibility of private physicians, eight of whom were general surgeons and eight of whom were gynecologists. We recognize clearly that 27 cases is a very small number, and therefore any conclusions drawn cannot be statistically significant; nevertheless trends are reflected.

Diagnosis.—Table III is labeled the Diagnostic Table, and here we have tried to correlate the symptoms, the preoperative diagnosis, and the various tests which were or were not carried out. With reference to this it is evident that although cervical cancer was not suspected, 17, or 63 per cent of the cases, presented a clinically abnormal cervix, and only 6, or 22 per cent of the cases, received the benefits of any extended preoperative investigation. It is also well to point out here that 25, or 93 per cent of these cases, had symptoms suggestive of cervical malignancy.

TABLE III. DIAGNOSTIC TABLE ACCORDING TO STAGES FROM 1922 TO 1951

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
No. Cases	3	13	6	3	2	27
<i>Preoperative</i>						
<i>Diagnosis.</i> —						
Cervicitis	2	7	2	3	0	14
Fibroids	1	7	3	1	2	14
Adnexal	1	0	0	1	0	2
pathology						
Prolapse	0	2	1	0	0	3
<i>Preoperative</i>						
<i>Study.</i> —						
Smear	2 (N)	1 (P)	1 (P)	0	0	4 (2P)
Biopsy	1 (N)	0	0	0	0	1 (N)
Curettage	1 (N)	0	0	0	0	1 (N)
<i>Symptoms.</i> —						
Discharge	1	7	3	1	0	12
Bleeding	2	7	5	2	0	16
Pain	0	3	0	1	2	6
Cervix	2	3	1	2	2	10
(Normal)						
Cervix	1	10	5	1	0	17
(Abnormal)						

Treatment.—Table IV indicates the method by which these patients were originally treated. Here it is interesting to note that in the first fifteen years of this study only one total hysterectomy was done, and this was done vaginally in a Stage I case. Three cervical amputations were done in other Stage I cases. One cervical amputation was done for a Stage II case, and one supravaginal hysterectomy was done in a Stage IV case.

In the last fifteen years, from 1937 to 1951, 15 of 21 cases, or 71 per cent, were managed by total hysterectomy, 2 vaginal and 13 abdominal. Three supravaginal hysterectomies were done, one in Stage IV, and 2 in Stage III, and these 3 records suggested diffuse pelvic inflammation, making the total

operation too hazardous. The remaining 3 cases in the years from 1937 to 1951 were treated by amputation of the cervix. One was Stage 0, one Stage I, and one Stage II.

TABLE IV. THERAPEUTIC TABLE ACCORDING TO STAGES FROM 1922 TO 1951

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
No. cases	3	13	6	3	2	27
Type of Operation.—						
Amputation of cervix	1	4	2	0	0	7
Supravaginal hyst.	0	0	0	2	2	4
Vaginal hyst.	0	2	1	0	0	3
Total hyst.	2	7	3	1	0	13

Pathology.—All of these patients demonstrated epidermoid lesions, and as can be seen in Table V the large majority of these tumors were considered to be representative of Grades II and III. From the point of view of anatomical location, in 18, or 67 per cent of the cases, the lesions were concealed, and in 9, or 33 per cent, the lesion was readily visible.

TABLE V. PATHOLOGICAL TABLE ACCORDING TO STAGES FROM 1922 TO 1951

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
No. cases	3	13	6	3	2	27
Location of Lesion.—						
Endocervix	3	7	4	2	2	18
Exocervix	0	4	1	1	0	6
Squamocolumnar junction	0	2	1	0	0	3
Type of Cell.—						
Squamous	3	13	6	3	2	27
Adenocarcinoma	0	0	0	0	0	0
Pathological Grade.—						
I	—	1	0	0	0	1
II	—	5	4	1	2	12
III	—	7	2	2	0	11
IV	—	0	0	0	0	0

Subsequent Therapy.—Following the initial treatment, and the subsequent surprise report from the pathology laboratory, the natural question is then "What further should be done?" In Table VI various methods employed for further therapy can be seen. Nine, or 33 per cent, received no additional treatment, and three of these were Stage 0, four Stage I, and two Stage II. All of these had previously had a complete hysterectomy. Two Stage I cases received subsequent radium, and three Stage I cases received subsequent x-ray. Eleven patients were later treated by both x-ray and radium. One Stage IV case received x-ray along with a presacral neurectomy for pain, and the remaining 3 patients were treated with a combination of x-ray, radium, and surgery. Two patients were re-treated by other methods. This accounts for the discrepancy in the figures of this table.

Table VII shows our end results. Because of the fact that our laboratory has only within the past three years looked favorably upon a diagnosis of intra-epithelial malignancy, 3 of our cases have to date a rather inconclusive follow-up. An additional 5 cases have not yet been followed for five years, and one patient is living at 4½ years, but is known to have disease. This patient had a coexisting cancer of the breast, and it is believed that her osseous metastases are from her breast disease. Regardless of these apologies, 14 of our patients, or 52 per cent, are alive and free of disease at the time of this report. Here, again, it must be borne in mind that these are not strict five-year survival figures.

In consideration of the stage of the disease we see in Table VIII that Stage 0 has a 100 per cent survival rate, Stage I has an absolute survival rate

of 77 per cent, and a corrected survival rate of 92 per cent. This allows for 2 deaths from causes other than cancer, the disease being apparently cured at the time of their death. Stage II has an absolute survival rate of 16 per cent, which corrects to 50 per cent. All of the patients with Stage III and Stage IV lesions were dead in under five years.

TABLE VI. SUBSEQUENT THERAPY ACCORDING TO STAGES FROM 1922 TO 1951

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
No. cases	3	13	6	3	2	27
No therapy	3	4	2	0	0	9
Radium						
Combined intracav- itary and interstitial	0	1	0	0	0	1
Intracavitary	0	1	0	0	0	1
Interstitial	0	0	0	0	0	0
Intraperitoneal	0	0	0	0	0	0
X-ray only	0	3	0	0	0	3
Radium and x-ray						
Combined intracav- itary and interstitial	0	3	4	1	1	9
Intracavitary	0	0	0	0	0	0
Interstitial	0	0	1	0	0	1
Intraperitoneal	0	0	0	0	1	1
Surgery and x-ray	0	0	0	0	PNR	1
					1	
Surgery, radium and x-ray	0	1	0	2	0	3

TABLE VII. FOLLOW-UP ACCORDING TO STAGES FROM 1922 TO 1951

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
No. cases	3	13	6	3	2	27
<i>Living and Well.</i> —						
1-5 years	3	4	—	—	—	7
5-10 years	—	1	1	—	—	2
10-20 years	—	5	—	—	—	5
<i>Alive With Disease.</i> —						
1-5 years	—	—	1	—	—	1
5-10 years	—	—	—	—	—	0
10-20 years	—	—	—	—	—	0
<i>Dead of Disease.</i> —						
0-1 years	—	1	1	1	1	4
1-5 years	—	—	2	2	1	5
5-10 years	—	—	—	—	—	0
<i>Dead of Other Cause.</i> —						
0-½ years	—	—	1	—	—	1
½-1 years	—	—	—	—	—	0
1-5 years	—	—	—	—	—	0
5-10 years	—	2	—	—	—	2

These survival figures are much more interesting and significant if they are evaluated in the light of what was done for them. Table IX shows this rather well. The top half of the chart is concerned with the original operation performed and the lower section of the chart shows that regardless of the type of original operation, and apparently regardless of the method of subsequent therapy, the stage of the disease when first seen is the main determinant as regards salvage.

TABLE VIII. SURVIVAL ACCORDING TO STAGES

	NO. CASES	SURVIVAL	
		ABSOLUTE (%)	CORRECTED (%)
Stage 0	3	100	100
Stage I	13	77	92
Stage II	6	16	50
Stage III	3	0	0
Stage IV	2	0	0
Total	27	52	67

TABLE IX. SURVIVAL FIGURES ACCORDING TO ORIGINAL OPERATION AND FURTHER TREATMENT

	STAGE					NO. CASES	% TOTAL	NO. LIVING AND WELL	SURVIVAL	
									% OF OPERATIVE SERIES	% OF TOTAL
	0	I	II	III	IV				% OF OPERATIVE SERIES	% OF TOTAL
Amputation of cervix	1	4	2	-	-	7	25.9	4	57	14.8
Supravaginal hyst.	-	-	-	2	2	4	14.8	0	0	0
Vaginal hyst.	-	2	1	-	-	3	11.1	2	67	7.4
Panhyst.	2	7	3	1	-	13	41.8	8	61	30
No therapy	3	4	2	-	-	9	33.3	6	67	22.2
Radium	-	2	-	-	-	2	7.4	2	100	7.4
X-ray	-	3	-	-	-	3	11.1	2	67	7.4
X-ray, radium	-	3	4	1	1	9	33.3	3	33.3	11.1
X-ray, surg.	-	-	-	-	1	1	3.7	0	0	0
X-ray, radium, and surg.	-	1	-	2	-	3	11.1	1	33.3	3.7

Comment

Dr. William Finn of Cornell published a very exhaustive review of a similar series in the April, 1952, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. He predicted that this entity of undiagnosed cervical cancer would increase in much the same ratio as cancer of the cervical stump would decrease. The reason for this prediction of course is the present trend toward the total as opposed to the subtotal operation.

Cancer of the cervical stump has been reported by various authors to represent from 2.5 to 11.3 per cent of their total cervical cancer series. The recent incidence in our clinic, according to Drs. DiLeone and Brown, has been 4.6 per cent, and the five-year survival figure in this series is 35.5 per cent. Our five-year survival figure for the clinic as a whole in reference to cervical cancer is 41.2 per cent, and Table X shows the comparative survivals for the entire series, the stump cases, the operative series, and the accidental surgical series.

TABLE X. COMPARATIVE SURVIVALS

	NO. CASES	5 YEARS SURVIVAL
Total cases 1933-1943	481	41.2%
Stump cases 1926-1942	31	35.5%
Cases operated upon 1922-1951	251	30.5%
Accidental cases 1922-1951	27	52.2%

Summary

This has been a preliminary survey of 251 cases of cancer of the cervix which were managed in part by surgery. Our incidence of operative treatment over the thirty-year period from 1922 to 1951 has been 21.4 per cent. We have attempted to divide these cases according to the type of operation performed and we have defined these surgical procedures as being accidental, palliative, investigative, and definitive. This report is concerned with our accidental series. Twenty-seven cases are discussed in detail. Sixty-seven per cent of these proved to be the responsibility of the private physician. Ninety-three per cent of the patients had symptoms of cervical cancer, 63 per cent presented with clinically abnormal cervixes and only 22 per cent were properly studied preoperatively. There were 3 Stage 0 cases, 13 Stage I, 6 Stage II, 3 Stage III, and 2 Stage IV. All of the cases were handled originally by operation, and in all cases the diagnosis was unsuspected. Sixty-seven per cent of the patients were given further treatment and we have tried to evaluate the survival figures in correlation with the original surgery, the subsequent therapy, and the stage of the disease. Further, we have stated that we believe this entity will be encountered with increasing frequency, and at the same time cancer of the cervical stump will be seen less often.

Conclusions

1. Unrecognized cervical cancer is becoming more prevalent because of the increased use of total hysterectomy.
2. In our experience the majority of these unsuspected malignancies are symptomatic and a determined effort should be made to arrive at a proper preoperative diagnosis.
3. There is at present no uniform method of handling these cases, and the survival results are directly proportional to the stage of the disease.
4. X-ray, selective radium treatment for local recurrences, and retroperitoneal node dissections should be given consideration. Naturally all cases are different and subsequent therapy should be individualized.

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CARCINOMA OF THE CERVICAL STUMP WITH SPECIAL REFERENCE TO THE CAUSES OF DELAY IN THERAPY*

Observations From Data of the Philadelphia Committee for the Study of
Pelvic Cancer

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THE successful management of cancer depends primarily upon early diagnosis. Any factor which delays the establishment of such a diagnosis may unalterably change a favorable prognosis to one that is adverse.

The Committee for the Study of Pelvic Cancer was organized in 1945 by the Obstetrical Society of Philadelphia with the sanction of the Philadelphia County Medical Society and the financial support of the Philadelphia Division of the American Cancer Society. The Committee was formed to study the delay period in the diagnosis of female pelvic malignancy. Thirty-five hospitals cooperate in allowing two experienced investigators to enter the wards and outpatient departments to interview all patients known to have pelvic cancer. A concise questionnaire is used to help record the desired information about the delay period.

Case histories with suspected physician delay are presented for discussion at a monthly luncheon meeting. Any physician who has been associated with the patient is invited to attend and discuss the problems of delay in a friendly fashion. A time interval of more than one month must have taken place between the patient's first visit to the physician and the achievement of the proper diagnosis before delay is said to exist. Previous reports^{1, 2, 3} have emphasized further details in the Committee's performance. Scheffey³ and Hahn² have stressed the fact that the highest percentage of cases where delay may be attributed to the physician occurs in the cervical stump group.

TABLE I. AGE INCIDENCE IN CARCINOMA OF THE CERVICAL STUMP

AGE GROUP	NO.	%
20-30	1	0.66
31-40	22	14.66
41-50	58	38.66
51-60	47	31.33
61-70	16	10.66
71-80	6	4.0
Total	150	100.0

The present study is concerned with patients who have a histologically proved invasive carcinoma of the cervical stump. Since its inception in 1945 to Sept. 1, 1954, 2,195 patients with carcinoma of the cervix have been investigated by the Committee for the Study of Pelvic Cancer. One hundred and fifty-three cases were classified as carcinoma of the cervical stump. Three of these were in situ carcinoma. This paper deals with the 150 histologically proved invasive carcinomas of the cervical stump, an incidence of 6.83 per cent among all cancers of the cervix.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Dec. 2, 1954.

TABLE II. RACE AND PARITY IN CARCINOMA OF THE CERVICAL STUMP

RACE AND PARITY	NO.	%
Negro	77	51.33
White	73	48.66
Parous	116	76.33
Nulliparous	34	23.66

Incidence

Age, Race, and Parity.—The age of the patients varied from the youngest at 29 years of age to the oldest at 75 years of age (Table I). The greatest incidence of cervical cancer occurred during the age period from 41 to 50 with 58 patients (38.66 per cent) in this category. There were almost as many patients, 47 (31.33 per cent) in the next decade (51-60 years). In most reports of cases of carcinoma of the cervix, as has been emphasized by Scheffey,⁴ there is usually an incidence of about 30 per cent of the patients who are 40 years of age or younger. In this present group of patients, all of whom had had the previous removal of a portion of the uterus, only 22 (14.66 per cent) were 40 or younger.

The racial distribution was about equal. Seventy-seven (51.33 per cent) were Negroes and the remainder (48.66 per cent) were white.

The greatest parity was vii in the 76.33 per cent parous women; the remaining 23.66 per cent were nulliparous (Table II). This figure corresponds closely to the 22 per cent cited by Redman.⁷

Symptoms.—There were 124 patients (82.7 per cent) who were first seen because of abnormal vaginal bleeding (Table III). This bleeding was usually first noted following trauma (coitus or douching) although the bleeding was not always associated with any traumatic episode.

TABLE III. SYMPTOMS IN CARCINOMA OF THE CERVICAL STUMP

CHIEF COMPLAINT	FREQUENCY
Abnormal bleeding	124
Vaginal discharge	20
Abdominal pain	2
Vaginal growth	2
Urinary incontinence	1
None	1

Vaginal discharge was the second most common symptom for which medical advice was sought. There were 20 patients (16.1 per cent) in this category. There were 2 patients who were seen because of abdominal pain, 2 who were conscious of vaginal growths, one who complained of urinary incontinence, and only one patient who had no gynecologic symptoms. This patient had been admitted to the hospital for medical management and a Stage I carcinoma of the cervix was detected on routine pelvic examination!

Stage of Disease.—Clinically there were about an equal number of patients in each of the international groupings (Table IV). There were 35 patients (23.3 per cent) in Stage I and 36 patients (24.0 per cent) in Stage II. There were 33 patients (22.0 per cent) in Stage IV, and the greatest number, 46 (30.66 per cent), were classified in Stage III.

TABLE IV. STAGE OF DISEASE IN CARCINOMA OF THE CERVICAL STUMP

STAGE	NO.	%
I	35	23.3
II	36	24.0
III	46	30.66
IV	33	22.0

There is such a diversity in the reports⁵ of the percentages of patients in the various international stagings that it is not possible to draw any conclusions from these distributions.

Associated Surgery.—Since the surgical procedures had been performed at various hospitals, many of them outside the city, and at varying times in the past, it was not possible to determine accurately in every case whether any associated surgery had been done in conjunction with the supravaginal hysterectomy.

When supravaginal rather than complete hysterectomies have been performed, the plea has been made that the complete operation had not been performed so that the operation would not be prolonged, or that the patient's general condition did not warrant further operative work. At least one third of the patients in this survey (Table V) had one or both adnexa removed and eleven appendectomies were performed. Ten bilateral salpingo-oophorectomies and three appendectomies had been done in patients with "coincident"* carcinoma of the cervical stump. Three plastic repairs, one "conization," 3 cauterizations without biopsy, and 2 diagnostic curettages were done. One patient had a trachelectomy carried out in conjunction with the supravaginal hysterectomy. In the latter case, a thorough review was done of all the removed tissues and it was decided that the carcinoma had arisen in the isthmus of cervix that remained after the combined abdominal and pelvic surgery had been completed. There was no evidence that this case belonged in the "coincident" group.

TABLE V. ASSOCIATED SURGERY IN CARCINOMA OF THE CERVICAL STUMP

Bilateral salpingo-oophorectomy	41
Unilateral salpingo-oophorectomy	9
Appendectomy	11
Plastic	3
Cauterization	3
Conization	1
Dilatation and curettage	2
Trachelectomy	1

Age at Hysterectomy.—In the patients who subsequently developed *true* carcinoma of the cervical stump, the average age at which the supravaginal hysterectomy had been performed ranged from 35.3 to 38.8 years (Table VI). The time which elapsed between the original operation and the discovery of the carcinoma of the cervical stump varied from 3 to 45 years. Twenty-four of the patients had not reached their thirtieth year when the hysterectomy had been done and 2 were in their late teens. The average time interval was 11.0 years in the "physician delay" group and progressed to 18.6 years in the "no delay" group. It appears that the longer the interval of time after hysterectomy the more likely the patient is to seek professional advice because of symptoms and the more likely the physician is to arrive at a proper conclusion.

TABLE VI. AGE AT HYSTERECTOMY IN CARCINOMA OF THE CERVICAL STUMP

	AGE AT HYSTERECTOMY	INTERVAL BEFORE DIAGNOSIS
No delay	35.3	18.6 years
Patient delay	38.7	15.4 years
Physician delay	36.1	16.8 years
Physician and patient delay	38.8	11.0 years
Physician delay (coincident)	43.0	9.6 months
Physician and patient delay (coincident)	42.7	11.0 months

*A "coincident" carcinoma is one which occurs within two years of the original hysterectomy and is presumed to have been present at the time of the operation.

In the "coincident" group, the average age of the patients at the time of hysterectomy was 43 years and the lapse of time before the discovery of the cervical malignancy averaged about 10 months. In 2 instances the squamous-cell carcinoma of the cervix extending upward into the endometrial cavity was discovered at the time of the histologic examination of the removed uterus and proper therapy was instituted reasonably soon.

Cause of Delay Period

In Table VII it is noted that the causes of delay are about equally divided among the four categories listed. As has been noted previously³ cervical stump cancer and vulvar cancer have the lowest percentage of cases in which there is no delay and the highest percentage of cases where the physician is considered to be largely responsible for causing the delay. In this present study the physician was deemed wholly to blame in 40 cases (26.66 per cent), institutional delay was actually responsible in 9 instances. The physician was thought to play a contributory role in diagnostic delay in 38 cases (25.33 per cent). An institution was fundamentally at fault 16 times.

TABLE VII. SOURCE OF DELAY IN CARCINOMA OF THE CERVICAL STUMP

CATEGORY	NO.	%	AVERAGE DELAY (MONTHS)
Patient	35	23.33	15.6
Physician	40 (9*)	26.66	8.7
Patient and physician	38 (16*)	25.33	17.7
No delay	37	24.66	
Total	150	100.00	

*Institutional delay.

The greatest average delay occurred when both physician and patient were culpable—17.7 months. When the patient alone was considered responsible, the duration of time was 15.6 months; and when the physician alone was to blame, the average length of time lost was 8.7 months.

The physician contributed to delay in 52 per cent of all the cervical stump cases. In 32 per cent of these cases (16.6 per cent of the entire group), however, the delay was institutional in origin rather than the fault of any one individual. Hahn² had noted a peak incidence of 60 per cent combined physician's delay in cervical stump cases and Scheffey³ observed that the greatest incidence of institutional delay (11 per cent) occurred in cervical stump cases.

When the physician was to blame for retarding proper therapy, two or more doctors were involved in 15 instances.

Cause of Patient Delay.—Patient delay, alone or in combination with physician delay, postponed prompt treatment in 48.66 per cent of the patients involved (Table VIII). It was not always possible to ascribe a reason for failure to seek medical advice. In those instances where a definitive type of answer was obtained, the fact that the initial bleeding was slight apparently served to minimize the possible dangerous origin of the bleeding. In 29 cases medical consultation was deferred since the patient thought the bleeding "not serious" or that "it would stop" or was natural or did not bother the patient. In 3 instances the patient either did not want to stop working long enough to see a physician or did not wish to pay for medical care. One patient incorrectly thought that the bleeding was rectal in origin, 3 just kept "putting it off," and 3 patients refused examination for varying periods of time until their symptoms progressed to such a degree that medical advice had to be sought.

TABLE VIII. CAUSES OF PATIENTS' DELAY IN CARCINOMA OF THE CERVICAL STUMP

Thought bleeding not serious	16
Thought bleeding would stop	10
Refused examination	3
Procrastination	3
Thought natural	2
Financial	2
Bleeding did not bother patient	1
Thought bleeding was rectal	1
Did not want to stop working	1

The essential cause for patient delay is lack of education in regard to the symptoms of the normal climacteric, the importance of abnormal bleeding or discharge, and the desirability of periodic complete physical examinations.

A routine inquiry was made into the educational background of the patients who were investigated by the Committee for the Study of Pelvic Cancer. In this particular group of patients very few had been exposed to more than a grade school education. In the category of patient and physician-patient delay, there were four who had a high school education, but this was almost exactly equal to the number of high school graduates in the other two groups of patients, so no conclusions may be elicited from this information. The increasing impact of the lay educational program of the American Cancer Society is extending even into the grade school and we may expect beneficial results in the future.

Cause of Physician Delay.—*Failure to examine the patient* when first seen is the most common error committed by the physician. This occurred 28 times (35.9 per cent) in the cervical stump series (Table IX). Pelvic examination may be omitted by the physician because of indifference on his part, because the patient is bleeding, because of lack of essential equipment to perform an examination, because of lack of time, or because of an idea that the bleeding may stop. Of course, all these explanations are inadequate and if the physician accepts the responsibility for the patient's care, he should either examine her adequately or refer her to another physician or a clinic where such an examination will be done.

TABLE IX. CAUSES OF PHYSICIANS' DELAY IN CARCINOMA OF THE CERVICAL STUMP

Failure to examine patient	28
Examined, lesion not recognized (douches)	21
Examined, curettage, no biopsy, no smear	12
Examined, cauterization, no biopsy, no smear	5
Examined, silver nitrate, no biopsy, no smear	4
Examined, other pathologic conditions obscured diagnosis	4
Carcinoma found, therapy delayed 3-22 months	3
Examination delayed, injections given	1

When the patients were examined, the *cervical lesion was not recognized as malignant* and douches were prescribed in 21 cases (26.9 per cent). Twelve patients (15.4 per cent) were examined and a diagnostic curettage performed *without a cytologic smear or a cervical biopsy*. Nine patients were examined, *no cytologic smear or cervical biopsy* done; 5 of these patients were treated with the electrocautery and 4 received multiple local silver nitrate applications for varying lengths of time before the true nature of the cervical disease was identified.

In 4 patients (5.1 per cent) fibromyomas were discovered on pelvic examination and the diseased cervix ignored as a source of trouble until a much later date.

In 3 patients (3.8 per cent) the proper diagnosis was made but proper therapy was deferred for 3 to 22 months because of failure of the institution to "follow through" on the diagnosis.

One patient received injections until subsidence of bleeding and then pelvic examination revealed an obvious carcinoma of the cervix.

The following case history demonstrates an extreme example of what can happen.

M. M., white, aged 50 years, para ii, consulted a physician in May because of a sudden episode of profuse vaginal bleeding. She was not examined, but was given oral medication. She was seen a number of times but the bleeding continued. She then was seen by another physician, not examined, but treated by various means. In January of the next year she was examined and hospitalization recommended. A short time later, a supravaginal hysterectomy was done because of myoma uteri. While convalescing from the operation she had rather profuse vaginal bleeding, so she was taken to the operating room and by means of an abdominal approach adhesions were freed and an abdominal packing was put in place. Then a pelvic examination was done, the cervix was found to be eroded, so it was cauterized and sutured. Later a biopsy of the cervix was interpreted as squamous-cell carcinoma so she was transferred to another institution for management of Stage IV carcinoma of the cervical stump (coincident).

Negligence in the performance of the cytologic smear or adequate biopsy of an abnormal cervix is a major cause of the ineffectual management of carcinoma of the cervical stump.

Subtotal hysterectomy should never be done until the cervix has been adequately studied prior to the abdominal surgery. It is equally unwise to accept a patient's assertion that all her female organs have been removed without making an adequate examination.

Survival

In any review of patients with malignancy, the success of treatment is usually measured by the number of patients surviving at the end of a five-year period. The patients in this study were treated at a number of institutions in the Philadelphia area by various methods, predominantly radiologic in nature. Since many of the cases studied have only recently been investigated, it was possible to utilize only 106 cases for this section.

In Table X the survival rates by category and stage are listed. Each group is of course quite small, but the trends are interesting.

In the "no delay" category 50 per cent of the 24 patients have survived. As expected, however, over half (15) are Stage I and II cases. The survival rate drops to 42.9 per cent in the "physician delay" group where there were 8 of 21 patients in the Stage I and II class, and progresses downward to 35 per cent in the "patient delay" category where only 5 of 20 patients were in the early stages of the disease! The lowest survival rate of the "true" cervical stump carcinomas is noted in the physician and patient delay column, and here there was an 11.8 per cent survival with only 3 of 17 patients considered to have early disease.

Of the 150 patients there were 30 (20 per cent) who had "coincident" carcinoma of the cervical stump. Twenty-four could be traced adequately. There was a 16.7 per cent survival in these patients with 4 cases listed in the Stage I-II division.

The over-all survival rate is 32.1 per cent and the survival rate of the true cervical stump cases is 36.6 per cent.

In a recent publication, reporting on the result of treatment of patients with carcinoma of the cervical stump, Hahn⁶ noted a survival rate of 30.8 per cent in true cervical stump cases and a like lowering of the rate to 13.3 per

cent in the "coincident" series. Redman⁷ reviewing a composite series, cited a 25 per cent five-year salvage in cervical stump carcinomas treated by irradiation and a 16 per cent five-year arrest in the "coincident" cases treated in a similar fashion.

TABLE X. SURVIVAL RATES IN VARIOUS CATEGORIES OF CASES OF CARCINOMA OF THE CERVICAL STUMP

	STAGE				TOTAL	%
	I	II	III	IV		
No delay	8	7	3	6	24	
Survival	7	4	1	0	12	50
Patient delay	1	4	8	7	20	
Survival	0	2	5	0	7	35
Physician delay	2	6	8	5	21	
Survival	2	4	3	0	9	42.9
Physician and patient delay	0	3	8	6	17	
Survival	0	0	2	0	2	11.8
Physician delay coincident	0	2	7	3	12	
Survival	0	1	1	0	2	16.7
Physician and patient delay coincident	2	0	6	4	12	
Survival	2	0	0	0	2	16.7
Total coincident	2	2	13	7	24	
Survival	2	1	1	0	4	16.7
Total	13	22	40	31	106	
Survival	11	11	12	0	34	32.1

Comment

The cervix is the most frequent site of pelvic carcinoma. When gynecologic surgery is necessary for the removal of the body of the uterus, the management of the cervix must be given proper consideration. Whenever hysterectomy by the abdominal route is contemplated, *the complete hysterectomy should be the operation of choice. The intelligent use of chemotherapy and antibiotics, the availability of blood and blood substitutes, the advancing knowledge of anesthesia, the better knowledge of anatomy and the improving training of the gynecologist make the complete hysterectomy possible with a minimum of risk.*

There are certain patients in whom extensive adhesions due to endometriosis or pelvic inflammation may make the complete operation most difficult. There are others who may be poor surgical risks because of associated systemic disease. In these few instances, the supravaginal hysterectomy might be considered, provided that careful cytologic study had been done and any disease of the cervix were properly treated, preferably by circular biopsy and endocervical resection. Following this type of operative procedure, the patient must of course be carefully examined at periodic intervals. It should again be noted that in this series of 150 patients, carcinoma developed in the cervical stump once after a conization and once after a trachelectomy.

It would appear likely that, with proper inspection of the cervix, careful cytologic study of the cervix, and adequate treatment for benign disease of the cervix, few stumps should remain to become cancerous in the future.

Summary

1. A brief résumé of the methods of the Committee for the Study of Pelvic Cancer is given.

2. One hundred and fifty cases of carcinoma of the cervical stump (an incidence of 6.8 per cent) are presented. There were 23.6 per cent nulliparous patients.

3. Vaginal bleeding and discharge were the most frequent symptoms.

4. The patients were fairly equally distributed in the different stages of the disease.

5. Over one third of the patients had some other type of surgery performed at the time of the hysterectomy.

6. The average age at the time of hysterectomy was 37 years in the "true" group and 43 years in the "coincident" group.

7. Combined physician delay was present in 52 per cent of the cases with an average of 13.1 months' delay. In 16.6 per cent there was institutional delay.

8. The most frequent cause of patient delay was delaying medical consultation since the bleeding symptoms were meager.

9. *Failure to examine* the patient was the most frequent cause of physician delay.

10. *Failure to recognize the cervical lesion* was the second most common cause of physician delay.

Failure to perform cytologic study and biopsy was associated with this error.

11. An average five-year survival rate of 32.1 per cent in all the eligible cases is recorded. There were thirty (20 per cent) "coincident" cases with a 16.7 per cent survival in the 24 eligible cases.

12. The importance of careful inspection, cytologic and biopsy study of the cervix is stressed. Total hysterectomy is emphasized as the hysterectomy of choice. In the rare instance when complete hysterectomy is not deemed wise, then the cervix should be properly treated before supravaginal hysterectomy and adequate periodic examinations must be continued in the future.

13. If the procedures recommended in the foregoing paragraph are accomplished, carcinoma of the cervical stump should become a medical rarity.

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LOW-DOSAGE ANDROGEN-ESTROGEN THERAPY FOR RELIEF OF THE MENOPAUSAL SYNDROME AND HYPOESTRINISM

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THE effectiveness and advantages of a low-dosage androgen-estrogen combination in the relief of symptoms of the menopause and of hypoestrinism have been demonstrated in 70 patients. I had previously administered these hormones in combination for the control of abnormal uterine bleeding¹ and to prevent pain and lactation in the puerperium.²

The objective of replacement therapy with estrogen has been to use the smallest amount of hormone possible to control symptoms of estrogen deficiency. Large doses of androgen have been avoided in gynecological practice in so far as possible because of the likelihood of masculinizing effects with extended use. In the use of androgen and estrogen in combination, low doses have been found to provide adequate relief of symptoms of the menopause and other estrogen deficiency states.³⁻¹² The small doses suffice since the hormones in combination exert a synergistic effect.⁶ With the hormones combined in a properly balanced ratio, neither the androgenic nor estrogenic effect predominates. This is an advantage because the undesirable effects sometimes encountered in single hormone therapy—uterine bleeding and arrhenomimetic effects—can be avoided.¹³⁻¹⁶

The combination of androgen and estrogen in tablet form used in the present study consisted of 5 mg. methyltestosterone with 0.02 mg. ethinyl estradiol. This is the combination used by Kupperman and Studdiford⁹ in the menopause and stated by McGavack¹⁰ to be sufficient as the daily dosage in a majority of climacteric patients. The results obtained, which will be described below, have compared favorably with those secured in menopausal patients by other investigators using larger doses of these two hormonal substances.¹⁷⁻¹⁹ It is interesting that combinations of even smaller doses of androgen and estrogen, such as 2.5 mg. methyltestosterone with 0.005 mg. ethinyl estradiol⁶ and 4 mg. methyltestosterone with 0.002 mg. ethinyl estradiol,^{7, 8, 12} have controlled the symptoms of the menopause and castration symptoms in younger women.

Material

Forty-nine menopausal or postmenopausal women ranging in age from 39 to 64 years were included in the study. In 7, the menopausal syndrome had developed following submission of the patient to various surgical procedures but none related to the ovary. One patient suffered from involutional melancholia. The symptoms present in each patient and their severity were carefully recorded before treatment. These included hot flashes, night sweats, dizziness, headache, depression, crying spells, and skin flushes. The symptoms

TABLE I. RELIEF OF SYMPTOMS OF THE MENOPAUSE AND OF

NO. PA- TIENTS	AGE RANGE (YEARS)	SYMPTOMS AND DEGREE OF SEVERITY (NO. PATIENTS WITH EACH)						DOSAGE
			HOT FLASHES	NIGHT SWEATS	DIZZINESS, HEADACHE	DEPRESSION, CRYING SPELLS	SKIN FLUSHES	INITIAL
<i>Menopausal Syndrome.</i> —								
49	39—1	Very severe	13	15	3	6	11	45 patients, 1 c.c. Gyne- tone Injec- tion
	40 to 49—29	Severe	13	5	6	6	20	
	50 to 59—16	Moderate	17	11	16	5	6	
	60 to 64—3	Mild	5	13	8	15	9	
		None	1	5	16	17	3	
<i>Hypoestrinism.</i> —								
21	24 to 29—4	Very severe	-	1	-	-	2	10 patients, 1 c.c. Gyne- tone Injec- tion
	30 to 39—13	Severe	5	3	2	2	4	
	40 to 42—4	Moderate	10	4	6	5	8	
		Mild	6	6	3	8	3	
		None	-	7	10	6	4	

varied in severity. The numbers of patients with each degree are recorded in Table I. Forty per cent of the symptoms encountered in the menopausal and postmenopausal patients were of a severe nature.

In addition, 21 patients with symptoms of estrogen deficiency received low-dosage androgen-estrogen therapy. These deficiencies were accompanied by, or resulted from, the following causes in the specified numbers of patients: castration, 4; ovarian resection, 3; ovarian cyst, 1; unilateral salpingo-oophorectomy, 4; hysterectomy, 1; Stein-Leventhal syndrome, 1; pituitary-thyroid-ovarian syndrome, 1; postpartum estrogen deficiency, 1; postoperative endometriosis, 1; and undetermined origin, 4. The patients in this group ranged in age from 24 to 42 years. Their symptoms resembled those of the menopausal patients. The severity of symptoms and numbers of patients with each degree are recorded in the table. Symptoms of severe degree occurred in 18 per cent of all those recorded.

Nothing remarkable was noted on pelvic or speculum examination in any of the 70 patients even though many of them had undergone surgical procedures. No patient was included in the series who had had a malignant growth removed surgically or in whom there existed a suspicion of malignancy.

Method

The androgen-estrogen preparation used for the initiation of therapy in 45 of the menopausal patients and 10 of the 21 patients with estrogen deficiency was a solution in oil containing 1 mg. estradiol benzoate and 20 mg. testosterone propionate in each cubic centimeter.* A dose of 1 c.c. was injected intra-

*Gynetone Injection. This and Gynetone Repetabs were furnished by Norman L. Heminway, M.D., Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

HYPOESTRINISM WITH A LOW-DOSAGE ANDROGEN-ESTROGEN COMBINATION

BIWEEKLY FOR ONE MONTH	RESULTS				SIDE ACTIONS	COMMENT
	EXCELLENT	GOOD	FAIR	POOR		
49 patients, 1 Gynetone tablet	25 (51%)	20 (41%)	3 (6%)	1 (2%)	1—severe 1—moderate (Dizziness, nausea, anxi- ety, appre- hension)	Involutional melancholia in 1 patient Menopausal syndrome devel- oped following operation in 7 patients
21 patients, 1 Gynetone tablet	15 (71%)	5 (24%)	1 (5%)	-	2—moderate (Dizziness, nausea, anxi- ety, appre- hension)	Castration, 4 patients Ovarian resection, 3 patients Ovarian cyst, 1 patient Unilateral salpingo-oopho- rectomy, 4 patients Hysterectomy, 1 patient Stein-Leventhal syndrome, 1 patient Postoperative endometrio- sis, 1 patient Postpartum estrogen defi- ciency, 1 patient Pituitary-thyroid-ovarian syndrome, 1 patient Undetermined origin, 4 pa- tients

muscularly at the start of therapy in each of these patients whose symptoms were severe. Injection therapy was not continued after the initial dose.

Each patient received twice weekly a so-called repeat action tablet containing 5 mg. methyltestosterone and 0.02 mg. ethinyl estradiol* and providing prolonged action of the two hormones. Tablet administration was continued with the bi-weekly doses for one month. The medication was then stopped and the results evaluated. If flushing, dizziness, night sweats, and other symptoms were not sufficiently alleviated, a second course of therapy identical with the first was given but in no case did treatment last longer than eight weeks. The patients received no other medication than the combined hormones parenterally and orally.

Results

Menopause.—The response to therapy was gauged by the subjective relief obtained. The result was judged to be excellent if all of a patient's symptoms disappeared, and good if all except one symptom disappeared. If a response to androgen-estrogen was noted but some symptoms persisted, the result was judged to be fair. In the absence of a response, the result was recorded as poor. The numbers of patients in each category are recorded in Table I.

Among the 49 menopausal patients, half were completely relieved of symptoms. All except one symptom disappeared from 20 additional patients. Therefore, a satisfactory response was obtained in 45, or 92 per cent, of this group.

A 41-year-old menopausal patient with involutional melancholia was severely depressed and had frequent hot flushes prior to the administration of the androgen-estrogen combination. Her symptoms were only partially allevi-

*Gynetone Repetabs.

ated by this therapy. So were the severe symptoms in one other menopausal patient. The severe skin flushing and mild symptoms in a third patient with only a fair response were partially relieved.

One 49-year-old menopausal patient, in whom all of the initial symptoms were extremely severe, noted no change while under treatment. She was one of the 4 patients in whom dizziness, nausea, anxiety, and apprehension were noted as side actions to treatment.

Hypoestrinism.—Under treatment, symptoms disappeared from 15 of the 21 patients who exhibited signs of estrogen deficiency. The 4 surgical castrates, 2 of the 3 patients with ovarian resection, and 3 of the 4 who had unilateral oophorectomy showed an excellent response. So did the patient with an estrogen deficiency post partum, the patient with Stein-Leventhal syndrome, the patient with postoperative endometriosis, and 3 of the 4 patients with estrogen deficiencies of undetermined origin.

Five patients with hypoestrinism were relieved of all except one of their symptoms—a good response. The patient with pituitary-thyroid-ovarian syndrome responded to treatment in this manner. Other patients who showed similar improvement included one with ovarian resection, one with an ovarian cyst, one patient who had a hysterectomy for massive fibroids, and one with an estrogenic deficiency of undetermined origin.

One 35-year-old patient had severe hot flushes and flushing of the skin. She was depressed and often had crying spells. Night sweats were mild and headaches and dizziness moderate in this patient. These symptoms appeared following right salpingo-oophorectomy and the Bell-Beuttner operation. They persisted despite therapy with androgen-estrogen. The patient had a moderate reaction to the medication. As in the other 3 instances, this consisted of nausea, dizziness, anxiety, and apprehension.

The over-all result among the 70 patients in this study with symptoms of estrogen deficiency was an excellent or good response in 65 (92.9 per cent), fair response in 4 (5.7 per cent), and no effect in 1 (1.4 per cent). Side actions occurring in 4 patients consisted of nausea, dizziness, anxiety, and apprehension of severe degree in one instance and to a moderate extent in the remaining 3. No uterine bleeding occurred as a result of treatment with the low-dosage androgen-estrogen combination (Gynetone) and no arrhenomimetic effects were apparent. The patients were pleased with the results of medication and cooperated readily.

Summary

An androgen-estrogen tablet containing 5 mg. methyltestosterone and 0.02 mg. ethinyl estradiol, constructed on the repeat action principle and designed to provide prolonged action, was used in the treatment of 49 menopausal or postmenopausal patients and 21 with deficiency of estrogen. Forty-five of the first group and 10 of the second, whose symptoms were severe, received initially 1 mg. estradiol benzoate combined with 20 mg. testosterone propionate in a single intramuscular injection. Among the 49 menopausal patients, the response was excellent in 25, good in 20, fair in 3, and poor in one. The response in the estrogenic deficiency states was excellent in 15 patients, good in 5, and fair in one. Side actions consisting of nausea, dizziness, anxiety, and apprehension occurred in 4 patients. This low-dosage androgen-estrogen therapy was concluded to provide adequate relief of symptoms of the menopausal syn-

drome and of hypoestrinism. In its use undesirable side actions of single hormone therapy, such as uterine bleeding and arrhenomimetic effects, were absent.

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1515 NORTH SECOND STREET

THE HYSTEROSCOPE

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ENDOSCOPIC examinations of the interior of the uterine canal together with endoscopic examinations of the adnexa have helped greatly in more accurate diagnosis of pathologic conditions of the uterine canal and the adnexa. Decker¹ and others have shown the value of culdoscopic examinations as an aid to diagnosis of disease in the adnexa and more recently endoscopic examinations of the uterine canal as done with the lens hysteroscope have proved valuable in diagnosing abnormal conditions in the uterine canal. We have used the present water hysteroscope in these examinations for seven years. It was first demonstrated in 1950.*

During the past seven years we have done one thousand hystero-grams or x-rays of the uterine canal in patients with uterine bleeding. When there has been seen a filling defect on the x-ray, then by means of the hysteroscope we have directly visualized the uterine canal, to determine the nature of the filling defect. The hystero-gram is thus not regarded as giving a final diagnosis as in the case of x-ray studies of the gastrointestinal tract, but is used only to determine whether the patient should have a hysteroscopic examination.

Rubin² for several years has done routine hystero-grams or x-rays of the uterine canal in all patients prior to a hysterectomy. We agree with him that all patients with uterine bleeding should have a hystero-gram, but in addition, if necessary, a hysteroscopic examination before any radical surgery. So often the patient with continued uterine bleeding and palpable serosal fibroids has a hysterectomy, and it is found following operation that the patient had functional uterine bleeding and the palpable serosal fibroids were incidental, since they did not protrude into the uterine canal.

Clinical Material

This report is a presentation of one hundred patients who have had a hysteroscopic examination. Fifty of these proved to have endometrial hyperplasia. Out of this 50, 20 showed filling defects in the x-rays that were suggestive of submucosal myomas or polyps, but nevertheless proved to be endometrial hyperplasia upon hysteroscopic examination.

Forty-three patients who had hysteroscopic examinations proved to have either endometrial polyps, submucosal myomas, or carcinoma of the endometrium.

Seven patients had a diagnosis of submucosal myoma with a very smooth filling defect seen in the x-ray. Hysteroscopic examination, however, proved that these patients had no submucosal fibroids and their bleeding was functional in origin, and required only curettage and not a hysterectomy.

*Certificate of Merit Award, American Medical Association, San Francisco, Calif., 1950.

From the study of one thousand hystero-grams in patients with uterine bleeding, we must conclude that an accurate diagnosis cannot be made from the x-ray alone. This series of one hundred hysteroscopic examinations illustrates also the difficulty of relying on bimanual examination and the curette to determine whether the uterus should be removed.

A hystero-gram and the hysteroscopic examination are also just as important in the patient with continued uterine bleeding, in whom, upon pelvic examination, nothing can be felt in the adnexa and the uterus is of normal size and free of serosal fibroids. Many of these patients are treated on an endocrine basis, when it is later found upon hysteroscopic examination that they have endometrial polyps or submucosal myomas that have been missed previously by repeated curettage.

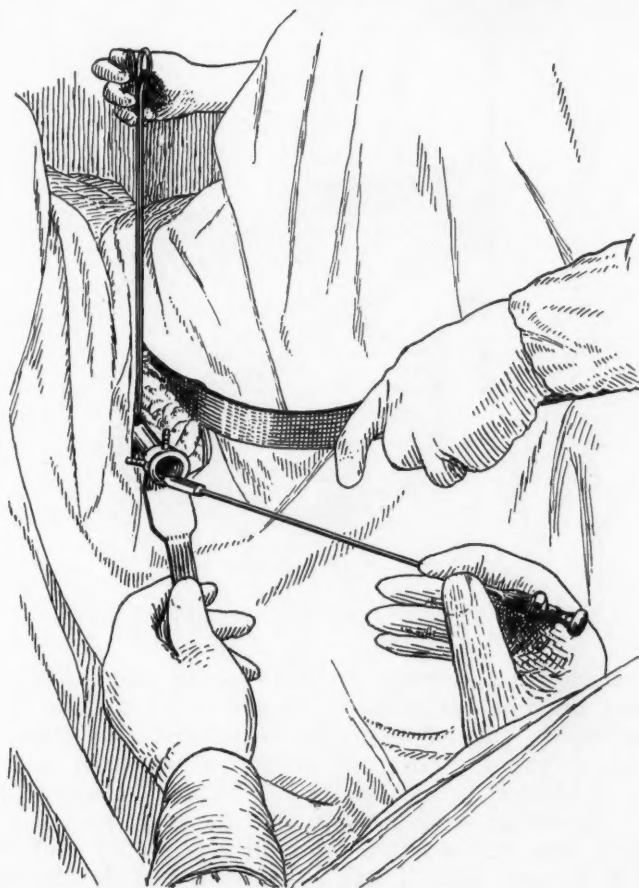


Fig. 1.—Metal sheath with obturator inserted in cervical canal. Withdrawal of obturator.

Technique

The technique of the hysteroscopic examination has been described previously,³ but will be reviewed briefly here to emphasize the simplicity of such an examination. The preparation is similar to that for a dilatation and curettage. A sound is first passed carefully through the cervical canal into the uterine canal, following which the cervix is slowly dilated with Hegar sounds and Goodell dilator to about the width for an ordinary curettage.

Following the proper dilatation of the cervix, the outer sheath of the hysteroscope* together with the obturator is inserted past the internal os, after which the obturator is removed, leaving the sheath intact in the cervical canal (Fig. 1). The lens system is then inserted into the metal sheath and locked in position (Fig. 2). The water connection is next made on the right. This flows from a container elevated above the level of the patient.

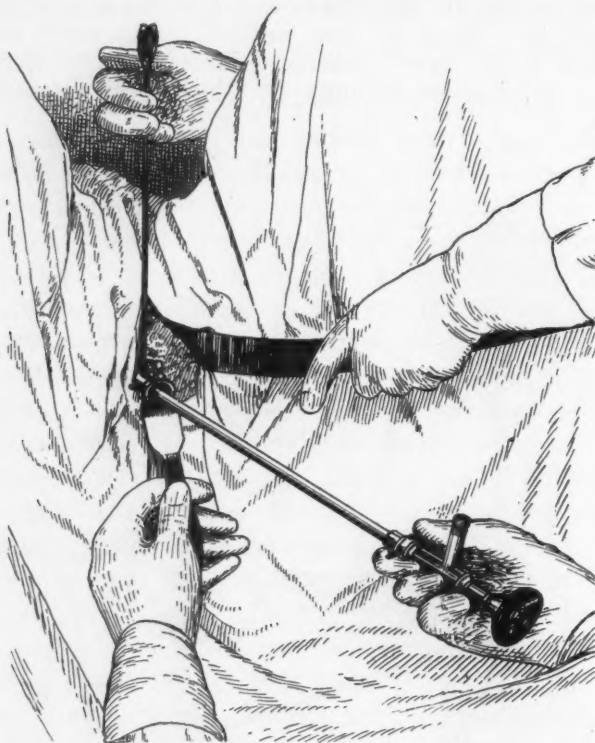


Fig. 2.—Insertion of lens system into metal sheath.

The light attachment and water connections are made as seen in Fig. 3. It is preferable that the light attachment be connected with a four-cell battery and that the battery be turned to nearly its capacity for good vision. After allowing the water to run and circulate in the uterine canal, it returns through the hysteroscope on the left as seen in Fig. 3. When the water upon its exit on the left of the hysteroscope is very clear, then the examination is ready to proceed. If the water flow on the left is running very slowly and does not have a forceful stream at its exit, then it will be necessary to elevate the container of water on the right to get enough water pressure to cause a rapid exchange of water in the uterine canal, thus insuring good vision.

The most important fact to keep in mind in a hysteroscopic examination is that the hysteroscope should be kept near the internal os as shown in a lateral view in Fig. 4. The failure to obtain clear vision is most often due to the fact that the hysteroscope is carried too far into the uterine canal, giving a very blurred view. The water outlet on the left of the hysteroscope should be closed at intervals with the gloved finger for clear observation. If, at the beginning

*The hysteroscope is manufactured by the National Electric Instrument Company, Elmhurst, Long Island, N. Y.

of the examination, the hysteroscope is kept near the internal os, and the uterine canal studied in this position for a while, then the hysteroscope may be gradually carried to the cornu under direct vision. It will be found that the entire uterine canal can be studied with very little difficulty. If upon inspection of the uterine canal a tumor is found, it is preferable that the hysteroscope be pulled backward toward the internal os to get a truer relationship as the hysteroscope will tend to magnify the tumor when it is very close to it.

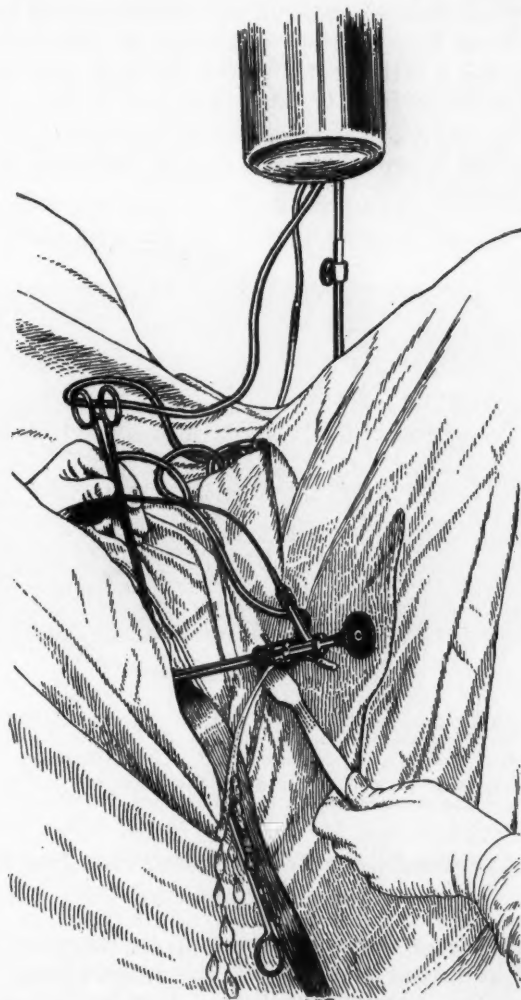


Fig. 3.—Hysteroscope inserted in uterine canal. Water enters on the right, circulates in uterine canal, and makes exit on the left of hysteroscope. Note that exit of water on the left is fast.

In women past the menopause the openings of the Fallopian tubes into the uterine canal may be observed. However, in the younger person the endometrium will often prevent accurate observation of the actual openings. The hysteroscope can, however, be carried easily into the cornu of the uterus and careful study may be made of this portion of the canal which is so often missed with the curette.

Fulguration of the Fallopian tubes at the entrance to the cornu can be done by carrying the fulguration tip through the channel of the hysteroscope under

direct vision, and fulgurating the orifices of the Fallopian tubes at the entrance into the uterine canal. However, we have not had a sufficient number of patients requiring this procedure to state whether such fulguration would produce permanent blockage of the Fallopian tubes. Fulguration of polyps in the uterine canal that have a very small pedicle is done with the fulguration tip similar to that used in the urinary bladder.

Biopsies may be taken through the hysteroscope under direct vision, although only a small amount of tissue may be removed in this manner. Recently, however, we have done biopsies of the uterine canal by first finding the area that we wish to take biopsy from, removing the lens system, and through the metal sheath inserting a large rectal biopsy forceps, and obtaining the specimen in the exact area of the uterine canal found upon hysteroscopic examination.

Photographs of the uterine canal in the living may be made through the hysteroscope by attaching a proper camera to the hysteroscope, and using time exposure for the best results.

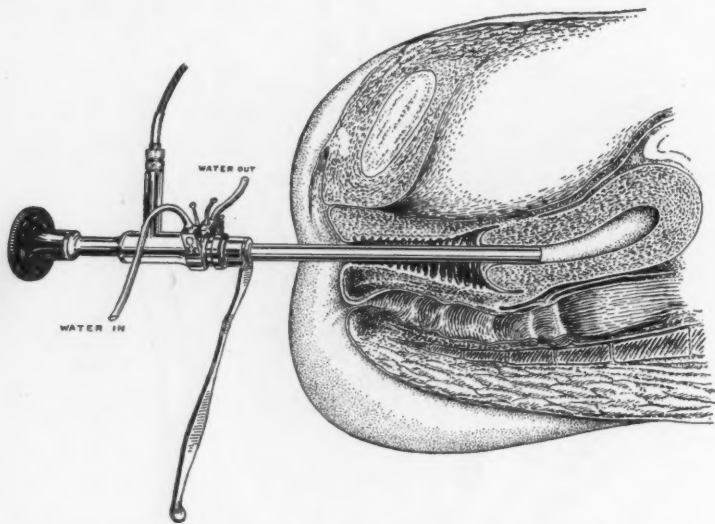


Fig. 4.—Sagittal section showing proper position of the hysteroscope in uterine canal near internal os. The hysteroscope may be carried up to the cornu.

Analysis of Types of Conditions Found in One Hundred Hysteroscopic Examinations

Endometrial Hyperplasia.—Fifty patients in this series of one hundred who had hysteroscopic examinations had endometrial hyperplasia. Of these, 20 patients, as previously noted, showed a filling defect by x-ray, but upon direct vision proved to have only endometrial hyperplasia (Fig. 5). The remaining 30 showed no filling defect, but because of persistent uterine spotting a curettage was undertaken. In this group, immediately following the curettage, examination by the hysteroscope showed that approximately 25 per cent of the endometrium remained.

Since there has been a question of danger of infection in the hysteroscopic examination, where only curettage and hysteroscopic examination are done and the uterus not removed, a follow-up of the postoperative findings in this group of 50 patients is noted. Of this group who had only hysteroscopic examinations and no abdominal surgery, it was found that no patient complained of abdominal pain or abdominal tenderness following this examination. The highest

temperature post-hysteroscopic examination was 99.8° F. There was no unusual bleeding postoperatively, other than that following an ordinary dilatation and curettage. There were no other complications observed.

Endometrial Polyps.—There were 14 polyps of the endometrium found by hysteroscopic examination in this group. The ages of the patients ranged from 31 to 66 years (Fig. 6). Eight of the endometrial polyps were removed by curettage, after the polyp had been localized with the hysteroscope. Four were removed by fulguration of the base of the polyp under direct vision. Fulguration of a polyp of the endometrium with a small pedicle may be done under direct vision in a way similar to fulguration in the urinary bladder. The larger polyps with wide bases require abdominal surgery.

Some of these patients had previously had repeated curettages, but the polyp had been missed with the curette particularly if the polyp was near the cornu. It is of interest to note that in several of the cases, after the polyp had been localized under direct vision, it was found very difficult to remove since the curette seemed to pass over it. Even larger polyps of the endometrium after having been localized with the hysteroscope were difficult to feel with the curette.

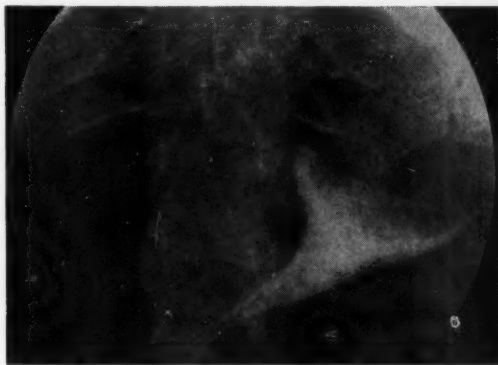


Fig. 5.

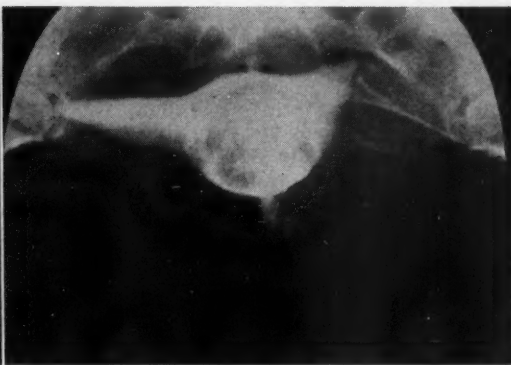


Fig. 6.

Fig. 5.—Smooth filling defect in top of hystrogram, suggesting submucosal myoma. Hysteroscopic examination proved the filling defect was endometrial hyperplasia.

Fig. 6.—Smooth filling defect in hystrogram. On hysteroscopic examination proved to be an endometrial polyp.

In this group of patients with endometrial polyps there was no elevation in temperature following hysteroscopic examination above that noted after the ordinary dilatation and curettage. In such cases, a curette or forceps will often miss a polyp, and it will then be assumed that the bleeding is on an endocrine basis. Many of these patients finally have a hysterectomy at which time an endometrial polyp that probably could have been removed under direct vision is found as the cause of bleeding. In many elderly patients the polyps may be removed by fulguration under direct vision, and hysterectomy may thus be avoided.

Submucosal Fibroids.—Patients with palpable serosal fibroids and associated uterine bleeding should have a hysteroscopic examination, since the uterine bleeding may be functional in origin and the serosal fibroids only incidental. Unless these fibroids protrude into the uterine canal they may not be the cause of bleeding. On the other hand there are many submucosal fibroids which protrude into the uterine canal with only a gradual elevation. Many of them are missed with the curette and the patient is treated on an endocrine basis.

In this group there were 25 submucosal fibroids found on hysteroscopic examination. Seven patients in this group had no palpable serosal fibroids, but

had submucosal fibroids found by hysteroscopic examination. There were 7 additional cases, previously mentioned, that were diagnosed as submucosal fibroids from the x-ray but were found upon hysteroscopic examination to be only endometrial hyperplasia. These latter patients, due to the fact that the filling defect was very smooth and also due to the fact that they had multiple palpable serosal fibroids, were advised to have a hysterectomy because of their persistent bleeding. After hysteroscopic examination, however, these 7 patients had only a curettage since the bleeding was found to be functional in origin and the smooth filling defect was caused by endometrial hyperplasia.

Submucosal fibroids protruding from the lateral wall with a gradual elevation were most often missed with the curette. It is extremely difficult to differentiate whether the curette is against a submucosal fibroid on the lateral wall or whether it is against the actual wall of the uterine canal. In the case of submucosal fibroids that protrude from the top of the uterine canal, it was nearly impossible to diagnose with the curette whether they protruded as a gradual elevation into the canal, or whether they protruded with a sharp elevation. This is the location where we most often found submucosal myomas that had been missed with the curette.

Endometrial Carcinoma.—There were 4 endometrial carcinomas proved by hysteroscopic examination and tissue examination. The carcinomas were of a whitish-pink color and were located near the cornu. The appearance of the carcinomas of the endometrium through the hysteroscope is different from the gross appearance when the specimen is removed for pathologic examination. In the biopsy the specimen is whitish gray in appearance in contrast to the shrimplike color in vivo.

There should be very little risk in doing a hysteroscopic examination on patients with endometrial carcinoma. There is no trauma to the endometrium as there is with the curette, since the hysteroscope stays near the internal os, and it does not come in contact with the lesion until the biopsy is taken. The risk of the irrigating water in a hysteroscopic examination carrying carcinoma-fous cells through the Fallopian tubes should not be any greater than in the routine hysteroqram.

Summary

A diagnostic test for tumors of the uterine canal is described and the results are summarized. A series of one hundred patients who had hysteroscopic examinations is presented to emphasize the simplicity of such an examination and its importance in detecting tumors of the uterine canal. A comparison of the hysteroqram or x-ray diagnosis with the hysteroscopic findings is given. No complication following hysteroscopic examinations in this group of one hundred patients or in any patient so examined in the past seven years has been noted. A hysteroqram or hysteroscopic examination is indicated in all cases of uterine bleeding as a diagnostic test to determine which patient should be operated upon and which should be treated for functional bleeding.

Hysteroqrames were made by Dr. I. Bird, Radiologist, Greensboro, North Carolina.

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Department of Case Reports New Instruments, Etc.

THE USE OF A TOURNIQUET IN UTERINE SURGERY

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A 12 INCH length of elastic rubber tubing may be used to check bleeding during the course of an intra-abdominal operation upon the uterus if it is applied as a tourniquet to the uterine and ovarian vessels. Such a tourniquet has been used in 34 operations, which would otherwise have been difficult or impossible to perform because of hemorrhage. In 33 instances nonmalignant tumors were removed from the uterus; in one additional patient, it was used to control hemorrhage from a ruptured cornual pregnancy.

The idea of applying a tourniquet to the uterus is not new. Bonney¹ devised a special instrument to control bleeding temporarily from the uterine vessels without crushing them. This was appropriately named the Bonney clamp. Davids² mentions the use of rubber tubing threaded through holes made in the broad ligaments next to the uterine vessels, pulled tight, and clamped to act as a tourniquet. Rubin³ describes the use of an elastic tourniquet which is similarly applied around the cervix. A No. 18 elastic rubber catheter was used as a tourniquet about both the ovarian and uterine vessels in the 34 operations here reported.

In order to include both the ovarian and uterine vessels in the tourniquet, any adhesions about the uterus, tubes, and ovaries must first be freed. Then the first assistant holds the uterus, tubes, and ovaries together in his cupped hands and pulls them gently upward. This enables the surgeon to slip the catheter around the infundibulopelvic ligaments beneath the assistant's finger tips. Traction on the tourniquet will then compress both the ovarian and uterine vessels against the cervix and the taut ends of the catheter can be crossed and clamped. The uterus may now be incised. If active bleeding occurs it means that the tourniquet is not tight enough.

The shortest continuous period the tourniquet was applied was twenty-eight minutes and the longest time was eighty minutes. There were no instances of embolism or of phlebitis following its use. Rubin recommends loosening the tourniquet every ten minutes. Davids and Bonney also state that it should be loosened during the operation. In all but one instance, the tourniquet was used for less than forty minutes. In the one prolonged appli-

cation of eighty minutes, it was not loosened because of the possibility of the uterine artery being lost. This patient later became pregnant and had an uncomplicated, normal labor.

Only once was it necessary to thread the tourniquet through a hole in the broad ligament. Prior surgery had resulted in the formation of adhesions between the left adnexa and the sigmoid. If the left ovarian vessels had been included in the tourniquet, part of the bowel would have been pinched. Instead, it was passed through an opening made in the left broad ligament. There was no bleeding in this case even though the left ovarian artery was unobstructed. Rubin and Davids use such openings regularly and note that bleeding is not troublesome with both ovarian arteries unsecured. Ordinarily we find it simpler to include the ovarian vessels in the tourniquet. When openings are made in the broad ligaments, they should be closed after the tourniquet is withdrawn.

The greatest use of a tourniquet is during myomectomy. It is noteworthy that the physicians who utilize myomectomy are those who have perfected a technique for hemostasis with special clamps or a tourniquet. There are many women for whom myomectomy is a desirable procedure. It is indicated to improve fertility, to save the uteri of women who hope for marriage and family, and for those individuals who would have a bad psychological reaction to hysterectomy.

Certain points need to be emphasized in reference to myomectomy. The uterine incisions should be planned so that as few as possible are made; often several tumors can be removed through a single incision. The incisions should avoid the tubes. It is usually advantageous to enter the endometrial cavity, first, to ensure that all submucous growths are removed and, second, to prevent formation of a sinus through an unrecognized and improperly closed opening. The injection of a small quantity of methylene blue prior to the operation will assist in identification of the endometrium. Finally, peritonization of the uterine incisions is important and if capsular peritoneum is deficient the reflected bladder or round ligament peritoneum may be utilized; occasionally a free omental graft is necessary.

Sometimes a tourniquet may be employed during a procedure other than myomectomy. Bonney mentions the use of his clamps in removing ovarian cysts. Four cases are reported to illustrate the use of a tourniquet: two involved multiple myomas of the interstitial and submucous varieties, the third is an instance of adenomyoma, and the last was a ruptured cornual pregnancy.

CASE 1.—A 29-year-old white woman was seen, after her first pregnancy had ended in miscarriage, with a tumor extending 8 cm. above the symphysis. Two years before she had had a multiple myomectomy performed elsewhere. When the abdomen was reopened, the uterus was found to contain seven myomas. The largest one measured 8 cm. in diameter. Adhesions were freed and a tourniquet was placed about the cervix. Incisions were made and the tumors were enucleated; the endometrial cavity was entered twice. The incisions were closed with interrupted sutures and peritonized by inverting the capsular peritoneum. The tourniquet was released and three spurting, bleeding areas appeared. These were

controlled with mattress sutures. The estimated blood loss was 250 ml. and the patient was given a transfusion of a pint of blood. Six months after the operation pregnancy occurred and went to term without complication. Delivery was spontaneous after 5 hours and 47 minutes of labor. Two years later there was no evidence of recurrence.

CASE 2.—A 33-year-old white woman who had been trying to conceive was found to have a fibroid mass extending 4 cm. above the symphysis. At the time of laparotomy, nine myomas were found. The largest one measured 7 cm. in diameter. After a tourniquet was placed, the tumors were excised; the uterine cavity was opened once. After the tourniquet was removed, no bleeding occurred. The estimated blood loss was 50 ml. Three months after the operation pregnancy occurred and went to term without complication. Delivery was spontaneous after 4 hours of labor. Three years later a second child was born after 2 hours and 40 minutes of labor. Three years after the second pregnancy, there was no evidence of recurrence of the myomas.

CASE 3.—A 37-year-old white woman was seen in premature labor during her third pregnancy. Two previous pregnancies had ended in miscarriage during the third month. There was a large tumor in the lower uterine segment. The tumor obstructed the third stage of labor and the placenta was removed instrumentally with difficulty. The child died shortly after birth. Eight weeks later the patient was subjected to laparotomy and a tumor which measured 10 cm. in diameter was found in the right lower uterine segment. A tourniquet was placed about the cervix and an incision made over the tumor. It could not be shelled out like a fibroid and was excised with some difficulty. The endometrial cavity was opened once. Once the tumor was out the operation was otherwise unremarkable. The pathological report was "adenomyoma."

CASE 4.—A 22-year-old Negro woman was admitted in the fourth month of pregnancy with a sudden, severe abdominal pain which had begun as a "tearing sensation" one hour previously. She was in shock and the abdomen was distended with fluid. At the time of laparotomy there was found a ruptured left cornual pregnancy with over 1,000 ml. of blood in the abdominal cavity. Membranes were bulging, and blood was pouring from an 8 cm. laceration in the uterine wall anterior to the left tube and round ligament. The pregnancy was evacuated manually and triplet fetuses and a placenta were removed. A tourniquet was quickly applied and the bleeding stopped. A layer closure of the uterine wall was then made. When the tourniquet was removed, no further bleeding occurred. The patient was given a transfusion of 3 pints of blood and the postoperative course was uneventful.

Conclusions

1. The use of a tourniquet as herein described has provided satisfactory hemostasis during myomectomy and other procedures.
2. There have been no complications as a result of use of the tourniquet in 34 operations. Pregnancy and normal childbirth are not only possible, but likely in selected individuals.
3. Physicians interested in myomectomy will find the tourniquet a useful device to prevent hemorrhage during the operation.

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THE UNCERTAINTY OF FETAL PROGNOSIS IN PREGNANCIES FOLLOWING Rh SENSITIZATION

A Case Report

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THE standard course of Rh sensitization and erythroblastosis fetalis and the prognosis for childbearing in women sensitized to the Rh factor are now generally understood. Classically, once an Rh-negative woman has become immunized and has delivered an infant with hemolytic disease, all subsequently born Rh-positive children will be affected, and as a rule will be more severely involved in each succeeding pregnancy; and, further, once a sensitized mother has been delivered of an erythroblastotic stillborn infant or a baby too severely affected to survive, there will be little hope for the survival of any future Rh-positive infant.

There is, however, an increasing awareness, among investigators who have a wide experience with fetal erythroblastosis, of the great tendency to deviation in either direction in the severity of the disease, which makes accurate prediction difficult, if not impossible, in many cases. That there is not sufficiently general appreciation of this variability is abundantly evident from the literature. This is well illustrated by the long list of measures advocated for the prenatal prevention or modification of erythroblastosis (vitamin C, competing antigens, diethylenesulfonate, exchange transfusion of the mother, "desensitizing" injections of Rh-positive blood, vitamin E, stilbestrol, progesterone and vitamin K, methionine, and Rh hapten). Most of these were enthusiastically presented, but all subsequently proved to be ineffective. The value of the most recently advocated of these therapies, the antenatal administration of cortisone, has also not been established, in the opinion of leading authorities.^{1, 2, 3} Hunter,⁴ the principal proponent of this therapy, in a recent report states, "It is important to observe that prior to the use of cortisone, we had never seen an Rh-positive child born alive of a mother who had previously had a stillbirth." In my experience, as in that of others, the conclusion implied in this statement is not valid.

An effective means of promoting a more widespread awareness of the great variability and unpredictability characterizing erythroblastosis fetalis might be the recording in the literature of selected illustrative case histories. An obstetrical history is presented which illustrates a great many of the more important variations in severity encountered in this condition, and which emphasizes the great difficulty of accurate prediction in the individual pregnancy.

Mrs. M. S., a 29-year-old gravida iii, para ii, was first seen on April 14, 1948. Her estimated date of delivery was July 16, 1948. It was found that she belonged to blood group AB, Rh negative (type cde/cde). The husband was group A, Rh positive (genotype cDE/c). Her first child, a male, belonged to group A, Rh positive (type cDE/c); and the second child, also a boy, was AB, Rh negative (type cde/cde). Serological studies for syphilis were negative.

Rh antibodies of the blocking type at this time, i.e., in the sixth month of her third pregnancy, were present in a 1:64 dilution of the patient's serum. This titer remained unchanged on repeated titrations throughout this pregnancy. On July 5, 1948, eleven days before her calculated term, labor developed and a hydropic stillborn male infant was delivered spontaneously. The skin was partially covered with golden yellow vernix. There was fairly general subcutaneous edema, the face was swollen with the edematous tongue slightly protruded, and the abdomen was distended. The enlarged spleen and liver were palpable well below the costal margin. Examination of the cord blood showed 1.28 million red blood cells per cubic millimeter, 5.39 Gm. of hemoglobin per 100 c.c. (color index 1.4), and 245 erythroblasts per 100 white blood cells. The clinical diagnosis of erythroblastosis fetalis of the congenital hydrops type was confirmed by the pathologist. The autopsy revealed fairly general anasarca, and effusion into the pleural and peritoneal cavities. The enlarged liver was studded with large foci of hematopoietic tissue consisting largely of erythroblasts and occupying slightly more space than did the liver cord cells, while the Kupffer cells were large and laden with hemosiderin pigment. The spleen was enlarged (25 grams) and overstuffed with hemosiderin pigment, and there was hemosiderosis of the kidneys. There was no evidence of birth injury, congenital malformation, or anomalies.

In her fourth pregnancy this patient reported on Nov. 21, 1949. The expected date of confinement was July 21, 1950. Blocking antibodies at this time were demonstrated in a 1:16 dilution of her serum. On Jan. 6, 1950, the titer had risen to 1:64 and this level was consistently maintained to her delivery date. On July 8, 1950, thirteen days before calculated term, labor was induced by minimal medical measures and she delivered spontaneously a female infant. This baby at birth exhibited pallor, with slight jaundice developing within a half hour. The spleen was palpable 2 cm. below the costal margin. Cord blood studies established her blood group as A, Rh positive. There were 2 million red blood cells per cubic millimeter, with the hemoglobin 7.7 Gm. and 53 erythroblasts per 100 leukocytes. The placental blood had been excluded by immediate clamping of the cord. One and one-half hours after birth, 15 c.c. of blood was withdrawn from the inferior vena cava through a polyethylene catheter introduced via the umbilical vein, and 55 c.c. of separated A, Rh-negative red blood cells were slowly introduced. No further blood was required. On the sixth day of life the red blood cell count was 5.11 million and the hemoglobin 16.9 Gm. A low of 2.49 million red cells and 8.2 Gm. of hemoglobin was reached at three weeks, followed by a gradual rise to 3.84 million erythrocytes and 12.3 Gm. of hemoglobin at 3 months of age. The jaundice reached its maximum intensity 18 hours postnatally, was then unchanged for perhaps 24 hours, after which it cleared rapidly. This infant thrived and made an optimal weight gain from the outset.

This mother first reported in her fifth pregnancy on June 21, 1951. The estimated date of confinement was Dec. 29, 1951. Blocking antibodies were then present in her serum in a titer of 1:64, a level that had been found two months prior to the onset of this pregnancy. This titer continued unchanged on frequently repeated titrations throughout the remainder of the pregnancy. On Dec. 23, 1951, eight days before calculated term, a female infant was delivered spontaneously. The amniotic fluid was deeply bile stained. At birth this infant exhibited pronounced pallor and there was considerable golden vernix. She was listless and weak. The spleen extended 5 cm. below the costal border and the liver was palpable. Jaundice was noted within a half hour, and its intensity increased for about twelve hours. It was definitely fading by the end of the second day, and absent at the end of the fourth day of life. The cord blood had 1.53 million red blood cells per cubic millimeter, 7.2 Gm. of hemoglobin per 100 c.c. (color index 1.5), 22,860 white blood cells per cubic millimeter, and 417

erythroblasts per 100 leukocytes. The baby's blood type was AB, Rh positive, and the Coombs test was positive. The icterus index was 130. The cord was immediately clamped to exclude the placental blood. Approximately 45 minutes after her birth, 25 c.c. of blood was withdrawn from the inferior vena cava through a polyethylene catheter introduced via the umbilical vein, and 72 c.c. of separated group O, Rh-negative red blood cells was very slowly transfused. Following this procedure the infant was normally pink and active. Her subsequent development was normal and additional blood was not needed. At 1 week the red blood count was 4.97 million and the hemoglobin 17.2 Gm. The lowest value for red blood cells, 2.79 million and for hemoglobin, 10.3 Gm. was reached at 7½ weeks, after which there was a progressive rise to 3.99 million red cells and 13.2 Gm. of hemoglobin at the age of 3 months.

This patient reported in her sixth pregnancy on Dec. 28, 1953. The estimated date of confinement was June 6, 1954. A blood sample at this first visit contained Rh blocking antibodies in a 1:64 dilution. The titer continued at this level through the date of her delivery. The indirect Coombs test was positive on the two occasions it was checked during this pregnancy. On April 30, 1954, 37 days prematurely, labor developed spontaneously and she was delivered of identical female twins that weighed 2 pounds 15 ounces and 3 pounds 13 ounces. Cord blood studies gave normal hematological values. Both infants were Rh negative (genotype cde/cde). Rh antibody was demonstrated in a 1:32 dilution of the serum of each baby, but the Coombs test in each instance was, of course, negative. Both infants have developed normally.

Blocking antibodies were still demonstrated in a 1:64 dilution of this mother's blood serum on Nov. 10, 1954, more than six months after the birth of the twins, suggesting that her anti-Rh titer probably is stabilized at this level.

Comment

The instructiveness of this history is enhanced, particularly in a period of restricted families, in that it carries through six pregnancies, encompassing the greater portion of the reproductive period of an Rh-immunized woman, thus affording opportunity for the sensitization pattern to develop adequately. A majority of the deviations from the usual and generally understood picture of erythroblastosis are portrayed in the obstetrical experience of this one individual.

The first significant variation was the unexpected severity of the disease in the first affected infant born to this mother, who was stillborn. The normal expectancy, of course, would have been for the first baby involved to have the disease in a relatively mild form. There was no history of blood transfusion or of blood given intramuscularly, and abortion even at an early stage could be excluded. As there had been but one preceding gestation, the first, in which the infant was Rh positive, this must have been solely responsible for the immunization of this mother prior to the pregnancy terminating in stillbirth. A review of this first or sensitizing pregnancy, and of the labor with its spontaneous delivery and uncomplicated placental stage, and the normal postpartum course, reveals nothing that might have accentuated the immunizing process.

On the other side of the picture was the unexpectedly favorable outcome of the two pregnancies (her fourth and fifth) which followed the stillbirth. Both infants, though quite severely involved, survived and were completely normal following a single transfusion of separated red blood cells. According to the widely held concept as reflected in the literature, there would have

been little hope that either of these infants would be born alive. These two cases, occurring successively, demonstrate that although the prognosis is admittedly grave in a pregnancy in which the infant is Rh positive, and with a history of a previous baby stillborn because of erythroblastosis, the outcome will be favorable more often than has been generally recognized.

Antenatal prognosis was further complicated by the occurrence of an Rh-positive infant in three successive gestations, actually in four of the first five pregnancies of this mother, whereas, with the husband established as heterozygous for the Rh factor involved, the mathematical expectancy was that 50 per cent of the infants might be Rh negative.

The maternal Rh antibody studies were likewise of little help in the antenatal prediction of the outcome of these pregnancies. There was, for example, no correlation between the maternal antibody titer of 1:64 attained in each of the four gestations studied, and the severity of the manifestations in the infants. This titer was unvaryingly present on frequently repeated titrations throughout all the pregnancies, with the exception of a single titer of 1:16 early in the fourth gestation. In the fifth and sixth pregnancies, moreover, the maternal Rh antibody titer of 1:64 consistently found on all of the determinations frequently repeated throughout both gestations, and known to be present also before the onset of the fifth, left us completely in the dark, until after the infants were born, as to whether they were Rh positive or Rh negative.

The unpredictability of the outcome of any given pregnancy, so well illustrated in this series of cases, clearly indicates the great difficulty of interpreting the results of treatment in erythroblastosis. Manifestly, any proposed new method of treating this condition must have widespread trial in large series of cases, with proper controls, before it can be evaluated.

Summary

The obstetrical history of a sensitized Rh-negative woman is presented, which illustrates the great tendency to variation in erythroblastosis fetalis, and emphasizes the difficulty of accurately predicting the outcome of any given pregnancy.

The need for a more general awareness of this variability and unpredictability is discussed, with the implications particularly for improved antenatal prognosis and the proper evaluation of proposed new methods of therapy.

The blood group studies on the mother and siblings and the antibody titrations on the mother were done by the Rh typing laboratory of the New York State Division of Laboratories and Research, which also confirmed the corresponding determinations and the Coombs tests on the infants.

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A NEW CONIZING AND BIOPSY KNIFE FOR THE UTERINE CERVIX

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THE purpose in designing this instrument evolves from the difficulties of present-day methods of obtaining biopsy specimens from the uterine cervix and of curing certain lesions.

The usual methods used today of obtaining biopsies consist of using the scalpel and taking quadrant specimens of the cervix or spot biopsies of suspicious areas seen grossly. In patients who have pathologic erosions, eversion, minimal lacerations, polyps, or endocervicitis, the cervix is then treated by electro-surgery with a conizing loop. These methods require two different steps, namely, one for biopsy with the scalpel, and one for treatment with the electrosurgical loop. One major drawback of the material obtained by these methods is the poor condition of the tissue. It is charred and carbonized, with the edema and distortion of the cellular structure making final microscopic diagnosis difficult and often impossible.

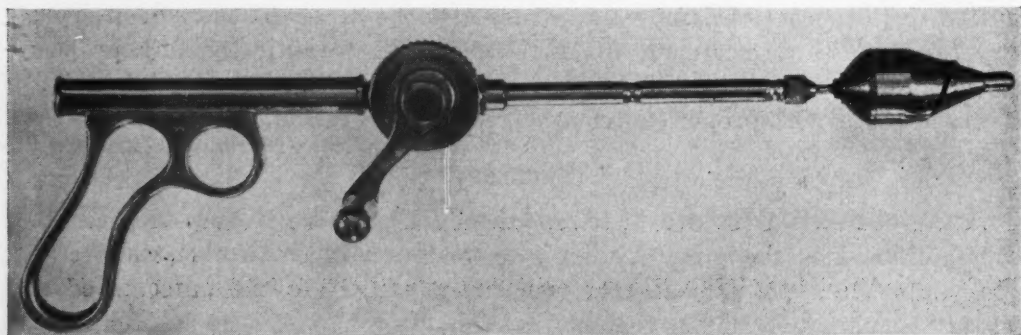


Fig. 1.—The circular conizing and biopsy knife for the uterine cervix.

The biopsy and conizing knife designed and shown here performs both steps (i.e., biopsy and treatment of the above-mentioned lesions) at one time. The instrument is made so that a continuous circular biopsy is made of the entire outer surface of the cervix as well as the endocervix by the circular cutting knife. By the rotation of this blade it also conizes or cuts out the pathologic area and removes it in the biopsied specimen.

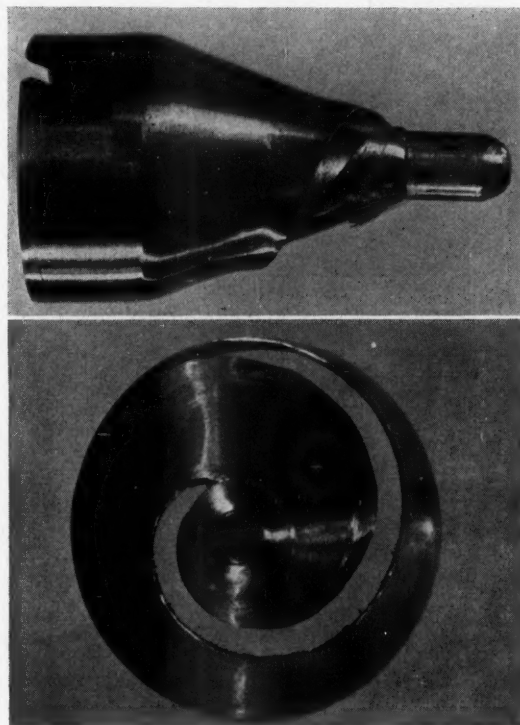
The material obtained is collected inside the cone-shaped cutting knife, from which all can be sent to the laboratory for complete laboratory diagnosis. Because it is collected by sharp cutting surfaces, it contains no carbonized tissue and the cellular structure is the same as it is in vivo. This allows the pathologist to examine completely the entire specimen and a more accurate final diagnosis can be made.

The conizing and biopsy knife causes no more bleeding than the ordinary scalpel or electrosurgical loop and it is readily controlled by electrocoagulation. Postoperative examination shows no evidence of cervical stenosis.

The instrument* will fit and adapt itself to cervixes of various sizes and the amount of biopsy material may be regulated to any depth or width of the cervix desired.

Technique.—The patient is prepared and draped in the usual manner for vaginal procedures. The cervix is then grasped by two Jacob's tenaculums on the lateral edges of the anterior lip of the cervix. The cervical canal is dilated, and a diagnostic curettage is performed.

A.



B.

Fig. 2.—The circular knife. A, Lateral view. B, Anterior view.

The conizing and biopsy instrument is then placed in the cervical canal with the axis of the instrument in line with the axis of the cervical canal. With traction on the cervix, the instrument is then turned, keeping firm pressure against the cervix. The number of revolutions of the instrument will be determined by the size of the conization and amount of biopsy material needed.

After conization, the cervix is inspected and bleeding points are coagulated with the electrocoagulator. The conizing knife is then unscrewed from the instrument and the biopsied material removed from the inside and sent to the laboratory for final diagnosis. A small gauze sponge or wick may be inserted into the cervical canal if desired. It is removed in 24 hours.

*This instrument is manufactured by George P. Pilling & Son Co., 3415 Walnut St., Philadelphia 4, Pa.

CHORIOCARCINOMA OF THE FALLOPIAN TUBE COINCIDENT WITH VIABLE PREGNANCY*

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SINCE choriocarcinoma usually results from a degenerative process which occurs during or following some form of pregnancy, it is exceptional that such a neoplasm should complicate a viable pregnancy. Our interest in this complication was aroused by the following case.

M. R. (Unit History No. 62460), a 27-year-old unmarried healthy Negro woman, was first seen in the Prenatal Clinic on June 25, 1954. As her last menstrual period had occurred on Jan. 6, 1954, her estimated date of confinement was Oct. 13, 1954. Her periods had been regular until her last menstrual period and she had had no subsequent bleeding or abnormal discharge.

The patient's past medical history was noncontributory. She had had two full-term uncomplicated vaginal deliveries in 1947 and 1948, respectively, and there was no history of previous abortions.

On physical examination no abnormalities were found except that the patient had failed to gain the proper amount of weight during this gestation. The size of the uterus was consistent with dates and the fetus was active. Laboratory studies were within normal limits. Her antenatal course continued to be normal in all respects prior to admission and she was last seen in clinic on August 13.

The patient was next seen at 7:00 P.M. on August 15, complaining of colicky pain in the lower abdomen of two hours' duration. There were no associated gastrointestinal or genitourinary signs or symptoms. There was no genital bleeding. The abdomen was soft, good peristalsis was audible, and the uterus was tender but not tense. Fetal heart sounds were distinctly heard. The cervix was closed and uneffaced. The hemoglobin was 11.3 Gm.; the leukocyte count was 9,000 with a normal differential. The blood pressure was 110 systolic over 70 diastolic and the pulse rate was 86. The patient was treated conservatively and during the next four hours her condition appeared to improve.

About 2:00 A.M. on August 16, she complained of generalized abdominal aching associated with a dull pain in both shoulders and in the pectoral areas. On re-evaluation the abdomen was found to be slightly distended, doughy to palpation, with minimal guarding and no rebound tenderness. Peristalsis was normal. On x-ray examination of the abdomen there was no free air or other abnormality found. While the laboratory findings and blood pressure remained the same, the pulse rate had increased to 120. Because of these findings a diagnosis of hemoperitoneum was made and an exploratory laparotomy was performed.

The peritoneal cavity was found to contain approximately 2,500 c.c. of fresh and clotted blood. The uterus was consistent in size with the duration of pregnancy and normal in appearance except for a reddish-purple, vascular mass at the right tubocornual junction (Fig. 1).

*Presented at a meeting of the Obstetrical Society of Philadelphia, Nov. 4, 1954.

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This mass was 5 by 3.5 by 2.5 cm. in size and blood was oozing from its uterine base. On inspection of all other viscera, no other bleeding point was found. Knowing the fetus to be alive, it was thought best to do a cesarean section and then excise the mass. A pallid 3 pound female infant was delivered by a Kerr cesarean section. The baby responded to minimal resuscitative measures and was transferred to the premature nursery.

While the uterus was open it was noted that the placenta was implanted on the left anterolateral wall and there was no gross evidence of penetration by the cornual mass. This mass, including a 1 cm. margin of normal tube and uterine wall, was resected. The patient's condition immediately following the operation was good.

On microscopic examination the specimen was found to be composed of two types of cells, cytotrophoblast and syncytiotrophoblast, which were intermingled with areas of hemorrhage (Figs. 2 and 3). No villi were identified. The diagnosis of choriocarcinoma was confirmed by Dr. Emil Novak and Dr. Arthur T. Hertig. Unfortunately, the placenta was lost in transit to the laboratory. The infant died seventy-two hours after birth from acute respiratory difficulties; at necropsy pulmonary hyaline membrane disease was found to be the cause of death.

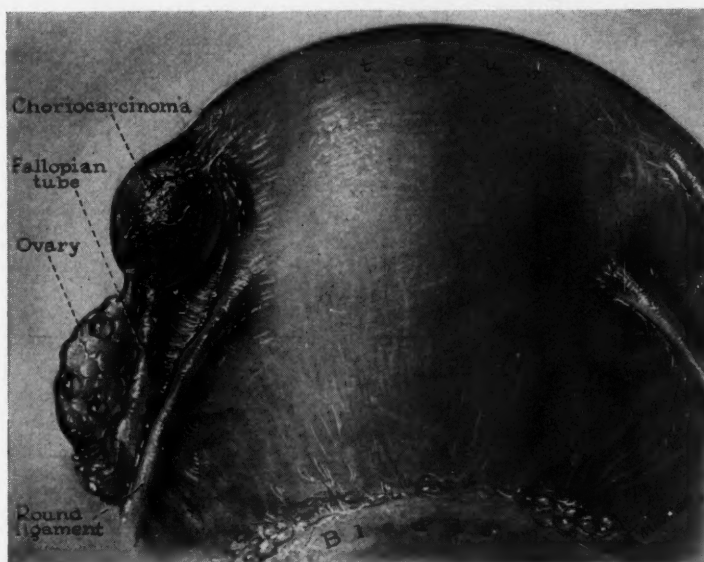


Fig. 1.—The tubal choriocarcinoma as seen at operation.

A serum gonadotrophin assay on the mother was positive in a dilution of one to ten; x-ray examination of the chest was negative for metastatic disease. On August 20, after the patient had received several blood transfusions, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed along with removal of the upper one-third of the vagina. Her postoperative convalescence was uneventful. On examination of over one hundred sections of the specimen there was no residual tumor found.

Biweekly determination of serum gonadotrophin levels remained positive in a dilution of one to ten until September 21 and since then they have been negative. Biweekly x-ray surveys and physical examinations have disclosed no evidence of metastatic disease. Because of the hemoperitoneum she was given 50 mc. of radioactive gold intraperitoneally.

Comment

Perusal of the available world literature disclosed that the development of choriocarcinoma during pregnancy coexistent with a normal fetus is an exceptional occurrence. The actual number of reported cases approximates ten.

Fig. 2.

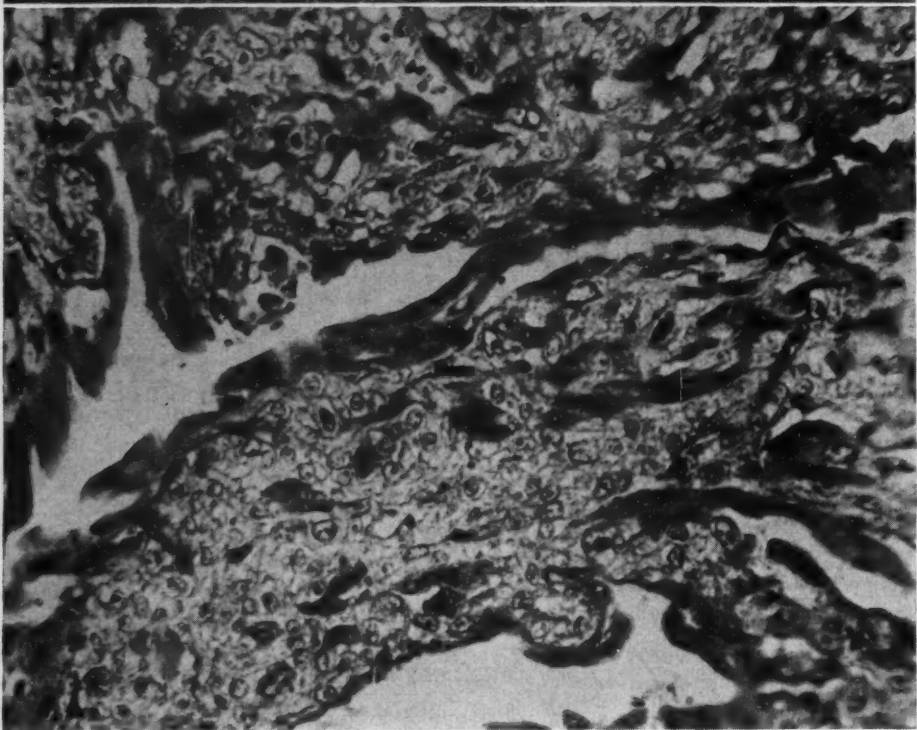
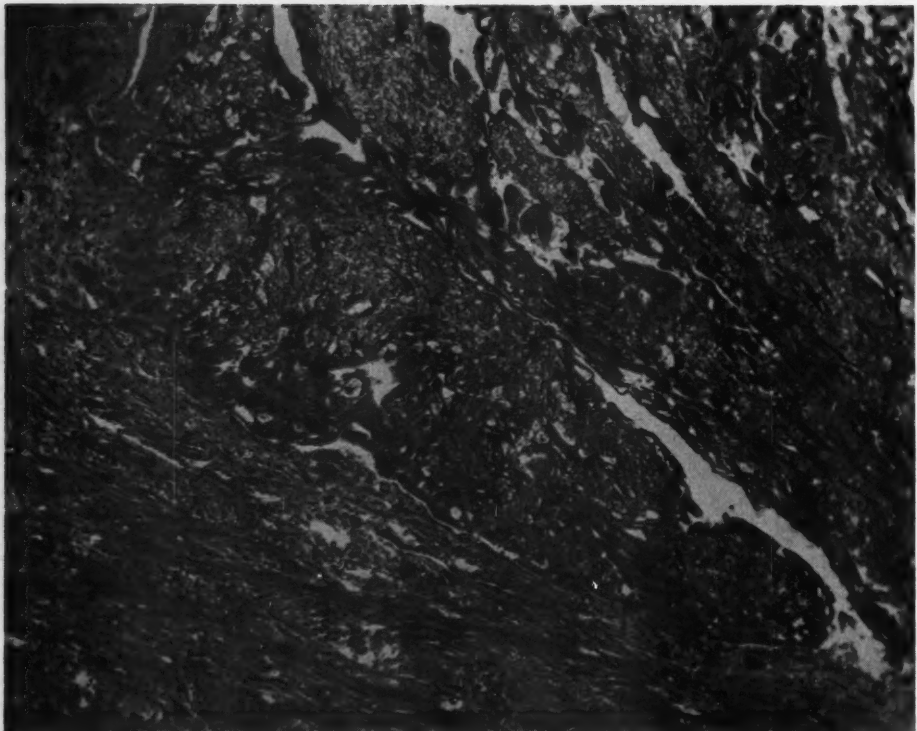


Fig. 3.

Fig. 2.—Masses of trophoblastic cells which have invaded the myometrium. ($\times 60$.)
Fig. 3.—The large cuboidal cytotrophoblastic cells and the flattened syncytiotrophoblastic cells are shown in their characteristic position in choriocarcinoma. ($\times 125$.)

It is noteworthy that in the majority of cases attention was called to the complicating tumor by hemorrhage. Genital bleeding from vaginal implants was the first abnormality noted in the cases of Walthard, Fikentscher, and MacRae; hemoptysis in Cordua's case; and hemoperitoneum in our case. A primary placental neoplasm was demonstrated in the majority of the previously reported cases. To our knowledge this is the first reported choriocarcinoma of the Fallopian tube to coexist with a living fetus. Resnick reported a choriocarcinoma of the breast complicating pregnancy. Other cases of choriocarcinoma complicating pregnancy have been reported by de Horlacher, Jacobs, Marchand, and Terada.

Many investigators have speculated concerning the origin of extrauterine choriocarcinoma. Williams classified these tumors as follows:

1. Those in which the tumor follows an ectopic pregnancy. He believed this to be the most common type of tubal choriocarcinoma.
2. Those which follow intrauterine pregnancy, the villi being transported to the tube during or subsequent to pregnancy without an initial malignant uterine lesion. Our case probably belongs in this group.
3. Those which are purely metastatic to an extragenital location from a primary growth in the uterus. This group satisfies the majority of cases of pregnancy concomitant with choriocarcinoma; and
4. Those which arise from chorionic cells in a teratoma. This group includes the greatest percentage of ovarian choriocarcinomas.

Hamdi suggested the possibility that the histogenesis of extragenital choriocarcinoma might be by metaplasia of rudimentary cell rests.

The ectopic type of choriocarcinoma of the tube without a primary tumor of the uterus is rare. That this possibility exists, however, is suggested by the reported cases of choriocarcinoma of the broad ligament in which there was no demonstrable primary tumor in the uterus.

Whether the neoplasm in this case arose from an early unrecognized ectopic or twin pregnancy, whether it originated from wandering villi from a previous pregnancy that remained dormant until stimulated by this pregnancy, whether it took origin from wandering atypical villi from the current pregnancy, whether it represented a secondary implant from a primary uterine neoplasm that had retrogressed or was not demonstrated, or whether it represented metaplasia of rudimentary cell rests is all material for conjecture.

The recognized treatment of choriocarcinoma is immediate removal of all the genital organs. Whether or not radiation methods also are utilized depends on the individual clinician's opinion.

The prognosis is uniformly poor despite the encouragement offered by negative hormonal titers, negative x-rays, and objective good health.

Summary

A case is reported in which a choriocarcinoma of the Fallopian tube coexisted with a living fetus.

Addendum.—The patient continued to do well until Nov. 16, 1954, when, on repeat x-ray survey, a 5 cm. density was found in the lower lobe of the right lung. A serum gonadotrophin assay was positive in a 1 to 10 dilution.

On November 21 she experienced a paroxysm of coughing which was accompanied by hemoptysis, dyspnea, and pain in the right chest. X-ray confirmed the physical findings of a right pleural effusion. Thoracentesis abated the symptoms. The fluid was positive for tumor cells.

On November 30 the patient was given 12.6 mg. of nitrogen mustard intravenously. She responded well as evidenced by a dramatic clinical improvement, the leukocyte response, and negative hormone titers. From December 10 to December 30, she received as an outpatient a total dose of 3,200 r over the anterior and posterior right chest.

Because of upper abdominal and right chest pain, she was readmitted on Jan. 3, 1955. On January 7, 10 mg. more of nitrogen mustard was given. Despite her subjective improvement, she became more cachectic and died on January 31, five and one-half months after her first admission.

Autopsy disclosed extensive metastases to the liver, lungs, and adrenal glands.

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AMNIOTIC FLUID EMBOLISM COMPLICATING LATE ABORTION

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NUMEROUS reports have appeared concerning the syndrome of amniotic fluid embolism. These papers have dealt with the problems of shock, anoxia, bleeding tendencies, and other effects of this dread maternal hazard. In those cases which ended fatally and in which postmortem examinations were made, the pulmonary findings of desquamated fetal squamous epithelium, lanugo hair, and fat droplets of the vernix have been tabulated.

This case presents a problem of the same category except that the maternal death occurred at an early stage of gestation.

E. M. B. (Hermann Hospital No. 53-18703), a 17-year-old Negro primigravida, was admitted to the hospital at approximately 24 weeks' gestation with the diagnosis of acute pyeloureteronephritis of pregnancy. Examination disclosed an oral temperature of 101.8° F., bilateral renal and flank tenderness, a gravid uterus the size of a 28 weeks' gestation, and a negative Homans sign. Urinalysis showed many white blood cells in the catheterized, uncentrifuged specimen.

The patient was placed on oral fluids and antibiotics. Twelve hours after admission she began to have uterine contractions. X-ray of the abdomen showed a twin intrauterine pregnancy. After a labor of approximately two hours, the patient was given $\frac{1}{150}$ grain of atropine by hypodermic injection and was taken to the Delivery Room. Under a general anesthetic of gas-oxygen-ether, a nonmacerated abortus and a liveborn infant that died five minutes later were delivered spontaneously without difficulty. The blood loss was considered to be above average but was not alarming (estimated at 400 c.c.). Shortly thereafter, the patient's oropharyngeal region became filled with a very frothy sputum. This soon became blood tinged and copious. The blood pressure was not obtainable and the pulse was 140 per minute. Despite suction, oxygen via nasal catheter, intravenous aminophylline, Cedilanid (digitalis), artificial respiration, and intracardiac Adrenalin, the patient died one and one-half hours post partum.

Autopsy revealed petechial hemorrhages of anoxia and massive pulmonary edema. Microscopic examination disclosed only a few syncytial cells in the capillaries of the alveoli and only a small quantity of refractile material in a few pulmonary vessels. Final pathological comment was that the case was compatible with amniotic fluid embolism, but that the typical intravascular debris was not demonstrable.

Inasmuch as the clinical signs and symptoms were so characteristic of the previously described cases of amniotic fluid embolism, an explanation for the cause of this paradox was sought. Many additional blocks of uterus, uterine veins, inferior vena cava, and lung were sectioned, but no distinct amniotic contents were found. A review of the literature disclosed that the reported cases had occurred at term or much nearer to term than this case.

It has been shown that, at this early stage of gestation, amniotic fluid does not contain appreciable amounts of squames, lanugo hairs, or fat globules.

Williams,¹ in his discussion of the microscopic detection of ruptured membranes, points out that this test is valueless prior to the thirty-second week of gestation because of the lack of demonstrable debris in the amniotic fluid. We verified this by the examination of ten samples of amniotic fluid from different periods of gestation. In no instance before the mid-third trimester were diagnostic particles present.

Comment

There are probably cases of amniotic fluid embolism which end fatally and in which the typical material is not demonstrated for various reasons. We believe that this case demonstrates the possibility of an amniotic fluid embolism occurring during the early periods of gestation and creating a diagnostic problem because of the normal absence of the expected amniotic fluid particles.

The sudden death in this case, due to acute pulmonary edema, and without mechanical obstruction of pulmonary vessels, tends to substantiate the argument for anaphylaxis in amniotic fluid embolism.^{2, 3}

Summary

A case of amniotic fluid embolism complicating late abortion is presented. The signs and symptoms were characteristic for this syndrome. However, initial postmortem diagnosis was difficult because it was not realized that the absence of desquamated fetal squames and fat droplets in the amniotic fluid may be normal at that early state of gestation.

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RUPTURE OF THE UTERUS*

Case Report

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RUPTURE of the uterus, dramatic complication though it is, does not demand that each instance be separately reported. During the course of a year at the Cook County Hospital, we will encounter approximately 5 such cases (an incidence of 1:2, 196¹). Most of these are of the typical variety, following known etiological factors and with a more or less typical train of symptoms. Occasionally, however, a case will arise of a rather "silent" nature. Two such cases were recently reported²; the present case represents the third in a short time.

Mrs. A. D., a 37-year-old white woman, gravida xv, para xi, was admitted on Oct. 13, 1954, in labor and delivered normally and spontaneously three hours after admission. The newborn infant weighed 8 pounds 12 ounces. The second stage of labor was of about ten minutes' duration. Prior to delivery it was noticed that the patient had very markedly enlarged varicose veins of the labia. After delivery, the placenta was expressed in ten minutes and was complete. Blood loss was estimated at about 150 c.c.

The patient's blood pressure during labor was 120/70. Immediately following delivery it was 90/70, which was the approximate level found during the prenatal course. The patient had experienced no unusual pain during labor or delivery. Two hours after delivery, the blood pressure was routinely checked and found to be 80/40, pulse 100 per minute. The blood loss continued to be small as in a normal puerperium.

Because of the moderate shock and because of the large veins of the labia and vagina which suggested the possibility of similar veins in the broad ligament with resultant hematoma formation, a sterile vaginal examination was deemed advisable. This disclosed a large defect in the right side of the lower uterine segment through which the entire hand could be passed. The perforation did not, however, enter the general peritoneal cavity.

With blood running into two veins and under the lightest of general anesthesia, the abdomen was opened. There was very little free blood in the peritoneal cavity. The trauma was visualized in the lower segment of the uterus on the right side. Here the peritoneal reflection was elevated and was discolored by the contained hematoma of about 300 c.c. A total hysterectomy was quickly performed. After the elevated peritoneal flap was opened, and the contained clots removed, the uterus was found to be perforated up through the entire length of the cervix to a point almost to the attachment of the peritoneal fold. In the excised specimen the rent measured 11 cm. Postoperatively the patient made an uneventful recovery without sepsis.

Comment

This case illustrates an aspect of the clinical complication of rupture of the uterus that has not been fully appreciated. The well-known episode which occurs following recognized causative factors, either during labor or

*Presented at a regular meeting of The Chicago Gynecological Society, Jan. 21, 1955.

delivery, needs little repetition. Everyone is cognizant of the fact that rupture has occurred when the patient experiences sharp pain, grips the lower abdomen, and falls back in shock, with the accompanying vaginal hemorrhage. What we are all prone to forget or neglect is the patient who rather silently develops a severe degree of pathologic rupture of the uterus without marked degrees of bleeding or shock. This is the patient who must have careful observation in the so-called "fourth stage of labor." A laceration of the genital tract should be suspected with any degree of depression of the blood pressure, especially in the "shock levels," with or without excessive bleeding which does not cease after the delivery of an intact placenta followed by proper oxytocic therapy. The possibility of laceration of the uterine wall should never be ignored because it has not been preceded by the commonly associated abnormalities of labor, operative procedures, or the usual symptoms. Certainly, it is even more likely following any of the well-known etiological factors.³

The fact that the patient presented such mild clinical symptoms in spite of the extensive laceration of the uterine wall (probably not involving major vascular branches) leads one to postulate that many cases of less severe complete and incomplete ruptures must assuredly go unrecognized. How important must these lacerations become, then, as precursors of future more serious ruptures of the uterus.

Summary

1. A case is presented illustrating the occurrence of uterine rupture of a severe degree without the dramatic symptoms usually associated with this condition.
2. Attention is drawn to the importance of strict observation of patients in the "fourth stage of labor" as regards nonresponding blood pressure in the shock levels, with or without excessive vaginal bleeding.
3. The severe degree of the uterine laceration with the minimal symptoms leads one to postulate that many cases of less severe rupture must go unrecognized and be precursors of later, more severe, rupture.

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HABITUAL ABORTION WITH PROLAPSE OF THE PLACENTA

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PROLAPSE of the placenta means the birth of the placenta before the fetus. This may happen both in cases of placenta previa and in cases where the site of the placenta is normal. Bureczak² has collected 46 cases of the latter type, 45 of the patients being multiparas while one was a primipara. Twenty-two of the infants were premature.

S. S., a 33-year-old gravida iv, para iii, was at term on Dec. 9, 1951. She had had two premature deliveries and one term delivery previously.

During her fourth pregnancy she was given intramuscular injections of Antefysin. No proteinuria or hypertension was noted during pregnancy. Two months before term on Oct. 4, 1951, at about 7 A.M., she suddenly fell ill with abdominal pain not resembling labor pains. There was an escape of liquor amnii, and she began to bleed per vaginam. On her admission to the hospital at 10 o'clock she was exhausted, almost in a state of shock. The placenta and membranes hung out of the vagina. At once she was given 500 c.c. of Macrodex, two blood transfusions, as well as penicillin. No fetal heart sounds were audible. The presenting part could be moved above the symphysis. At 11:20 A.M. she was delivered spontaneously by breech presentation of a dead female fetus that weighed 1,820 grams. On admission there was a trace of albumin in the urine, which was normal at later examinations. The puerperium was normal, and the patient was discharged well.

On July 4, 1953, she was delivered spontaneously of a live female infant that weighed 3,210 grams.

Comment

Probably a normally inserted placenta prolapsed in 1951. The diagnosis might have been confirmed by a histological examination of the placenta, and the demonstration of fibrinogenopenia during labor. However, by cesarean section it has been demonstrated that premature separation of the placenta may occur simultaneously with placenta previa.^{1, 3, 5, 6} The diagnosis consequently may be difficult. Kobes⁴ searched for remains of the placenta and found its insertion in the fundus uteri. Palpation of the uterine wall is probably the only reliable method of deciding whether we are dealing with the prolapse of a normally inserted placenta or a placenta previa.

Summary

A case of prolapse of the placenta is reported. Placenta previa and premature separation of the placenta may occur simultaneously, and it is not possible to decide with certainty which type of prolapse occurred in this case.

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ERYTHROBLASTOSIS (HYDROPS) FETALIS FROM KELL SENSITIZATION

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IF POSSIBLE cases of OAB incompatibility be excluded from consideration, approximately 98 per cent¹ of cases of erythroblastosis fetalis are in the classic pattern of the Rh-negative mother sensitized against the Rh factor and pregnant with an Rh-positive fetus. Routine tests based on this concept confirm diagnoses in almost all cases of erythroblastosis and, if performed antenatally as is done at this hospital, permit almost uniform anticipation of cases. An occasional case is recognized, however, only as past obstetrical history, past history of transfusions, or clinical suspicion prompts special studies. Ideally, such special studies seek to demonstrate (a) the presence of atypical antibodies, (b) the specificity of such atypical antibodies (most often these prove to be anti-hr' [anti-c]), and (c) homo- or heterozygosity of the husband for the factor involved. Few cases of hydrops fetalis from Kell sensitization alone have been previously recorded. Race and Sanger² list two families with hydrops fetalis due to Kell sensitization alone together with five others in which hemolytic disease of the newborn was seen. Thus, as in the case below, sensitization to the Kell factor, though not common, may have severe effects.

Case Report

Mrs. R. C., gravida iii, para ii, Blood Group A, Rh-negative (ede), came under observation in May, 1954, when six weeks pregnant. The first pregnancy in 1947 was uneventful except for postpartum hemorrhage which was treated with an infusion of 500 c.c. of normal human plasma. The second pregnancy in 1949 was uneventful, four tests of the mother for Rh sensitization disclosing no evidence of anti-Rh or anti-Hr antibodies. The present pregnancy proceeded apparently uneventfully with four tests for Rh sensitization showing no antibodies until it was observed in October (thirty weeks' gestation) that the uterus seemed larger than expected. In November (thirty-four weeks' gestation) spontaneous rupture of the membranes occurred and the patient was hospitalized. Fetal heart tones seemed of good quality before she went to the X-ray Department but were no longer audible upon her return. The x-ray (Fig. 1) showed a large fetus with a "halo" about its body (dotted lines indicate part of the halo) and a diagnosis of hydrops fetalis was made. The patient delivered a stillborn infant the same day. Recovered amniotic fluid measured 3,500 c.c. The placenta was large and grossly edematous.

The stillborn fetus was a female, weight 2875 grams, crown-heel length 41 cm. The body was markedly edematous, with free fluid in the body cavities, and showed the typical findings of hydrops fetalis including marked extramedullary erythropoiesis in the liver and spleen. The cord blood was of Group O and Rh positive.

Special laboratory studies were started as soon as the x-ray findings were known. These established the diagnosis of anti-Kell sensitization. The details of the study follow. Blood specimens obtained from Mrs. C. were confirmed as Group A, Rh negative (cde) and from Mr. C. as Group A, Rh positive (CCDe). Mrs. C.'s serum was free of anti-Rh antibody but contained an atypical antibody, agglutinating her husband's cells but the cells of only one of ten random Group O, Rh positives and of none of three random Group O, Rh negatives. Titer of the atypical antibody against the husband's cells was 4 (saline tube test method), 8 (high protein tube test method), or 64 (anti-human serum tests of progressive saline dilutions). The mother's serum agglutinated the stillborn infant's cells. The cord blood, in addition, showed positive reaction with the Witebsky coating tests as well as the direct reaction (Coombs test) with anti-human serum.



Fig. 1.

Formal delineation of the atypical antibody as anti-Kell (anti-K) is shown in Table I. Mrs. C.'s serum reacts in parallel with a known anti-Kell serum.

TABLE I

CELLS OF	AGAINST SERUM	
	KNOWN ANTI-KELL	MRS. C.
Mrs. C.	Negative	Negative
Mr. C. and the 2 living C. children	Positive	Positive
Mr. C.'s mother (Group B)	Positive	Positive*
Stillborn infant	Positive	Positive
Four Group O, Rh Negative (cde)	Negative	Negative
Four Group O, Rh Negative (cde)	Positive	Positive
Nine Group O, Rh Positive	Negative	Negative
One Group O, Rh Positive	Positive	Positive
Two Group O, Rh ₀ 'Rh ₀ " (CcDE)	Negative	Negative

*After absorption of anti-B antibodies.

The identification of the atypical antibody as anti-Kell (anti-K) permitted establishment of the husband as homozygous positive for Kell when his cells were tested with anti-Cellano (Anti-k) serum obtained through the kindness of Dr. Philip Levine. The negative reaction between the husband's cells and the anti-Cellano serum³ establishes the husband as being genotype KK so that all children born to this couple in the future will be Kell positive and presumably erythroblastotic.

A case of this type emphasizes the need for clinical alertness. The laboratory cannot as a routine in all obstetrical cases perform all of the tests necessary for all of the theoretical causes of erythroblastosis. Thus it becomes the responsibility of the clinician to initiate special studies, particularly in cases where clinical evidence alone raises the possibility of erythroblastosis. It then becomes the responsibility of the laboratory to carry through and establish or disprove the suspicion.

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Editorial

IN THIS issue there appears the translation of the article by Rudolf Spanner on "The Circulation of the Human Placenta." The original of this treatise was first published in German in 1936. It is now being republished in translation as the first of a series in which articles will appear that have come to be regarded as classics or have marked some milestone in the development of our specialty.

This proposed series represents the trial of a new policy. The Editors, however, feel that this is a worth-while experiment. Many of the great contributions to obstetrics and gynecology are known to the present generation only in part or in the form of brief quotations. Their reappearance represents an honor to the original contributor and a sign of respect to our own history.

The continuation of this policy will be dependent upon reader approval. The Editors invite letters commenting on the value of this step and suggestions as to those articles of significance which might be published here in the original English or in translation.

The Editors

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Selected Abstracts*

American Journal of Medical Sciences

Vol. 229, April, 1955.

*Finnerty, F. A., Jr., and Sites, J. G.: The Value of Parenteral Reserpine in Acute Hypertension, p. 379.

Finnerty and Sites: Value of Parenteral Reserpine in Acute Hypertension, p. 379.

The authors treated 162 pregnant patients with acute hypertension due either to toxemia of pregnancy or to essential hypertension. The optimal dose of reserpine was found to be 2.5 mg. Eighty-six patients were given a single injection (intravenous, usually) of the drug and five others had multiple injections at 8 to 12 hour intervals. No other therapy was used in this group (56 per cent of the series), because of the satisfactory response. When, after two hours, reserpine was found to be ineffective or more vigorous therapy seemed indicated, other hypotensive drugs were added. "Alternate patients" are said to have been given intramuscular Unitensin and the others intravenous 1-hydrazinophthalazine, but 47 received reserpine plus Unitensin while 24 received reserpine plus 1-hydrazinophthalazine. Intravenous reserpine alone requires at least an hour and usually about two hours to exert its maximal hypotensive effect; the average drops in blood pressure were 23.5 (10 to 50) mm. Hg in the systolic and 19.4 (10 to 80) in the diastolic pressure. The duration of response was 2 to 16, average 6.5 hours. Reserpine potentiates the sedative action of the barbituates, prolongs the action of the Veratrum preparation, and enhances the hypotensive action of the 1-hydrazinophthalazine. Thus the use of reserpine reduces the dosages of the other drugs and minimizes their toxic side effects. Reserpine allays anxiety and nervous tension and "if parenteral reserpine had no hypotensive effect at all, it would still be an important therapeutic advance."

LEON C. CHESLEY, Ph.D.

Archives of Surgery

Vol. 69, October, 1954.

*Gray, Laman A.: The Case for Hysterectomy, p. 500.

Gray: The Case for Hysterectomy, p. 500.

Unfortunately the author has chosen a name for this study that suggests special pleading for this operation. This gives an erroneous impression, for the presentation is a well-balanced analysis of 1,075 private patients subjected to this operation for a variety of reasons.

*Titles preceded by an asterisk are abstracted below.

The indications for operation are codified in a conventional manner except for a category called "combined syndrome" which includes patients with several pelvic abnormalities, none of which individually add up to an indication for operation but together were considered significant enough to warrant it. This group makes up approximately 25 per cent of the total and is perhaps the area where judgment is rightly said to be most difficult and would perhaps be controversial among different schools of gynecologic thinking. It is of some interest that in the entire series an incidence of 1.8 per cent unsuspected malignancy was encountered in the excised tissue.

The author refers repeatedly to patients with nervous symptoms who failed to benefit from operation or who failed to admit benefit from operation and he quite properly states the serious problem involved in selecting from such a group of patients who require surgical treatment. A mortality rate of 0.3 per cent occurred in the total series. This fact, together with the postoperative morbidity in any hysterectomy series, makes one perhaps somewhat reluctant to accept beliefs concerning the constant superiority of hysterectomy over radiotherapeutic castration for dysfunctional bleeding without more data than can be obtained from such a study.

S. B. GUSBERG, M.D.

Vol. 69, November, 1954.

*Markle, J. B., IV: *Struma Ovarii*, p. 756.

Markle: *Struma Ovarii*, p. 756.

The author briefly mentions a few fragments of the literature concerning struma ovarii and then presents one interesting case of his own; the patient, aged 23, was noted to have an ovarian cyst. Examination of the specimen following removal showed it to be a cystic teratoma composed entirely of thyroid tissue. Unfortunately, no studies of thyroid function were made in this patient.

S. B. GUSBERG, M.D.

Boletin de la Sociedad de Obstetricia y Ginecologia de Buenos Aires

Vo. 33, September 9, 1954.

*Miranda, V. Rodriguez: *Obesity, Pregnancy and Nutrition*, p. 269.

Albertelli, Jorge F., and Monaco, Horacio: *Survival in Partial and Total Pelvic Exenteration*, p. 274.

Di Fonzo, Normando Oscar, Serfaty, Salomon Oscar, Repetto, Eduardo David, and Torterola, Tomas: *Spontaneous Rupture of the Uterus at the End of Pregnancy*, p. 283.

Miranda: *Obesity, Pregnancy and Nutrition*, p. 269.

This article starts with the assumption that most obesity is alimentary rather than endocrine in origin, and defines the obese gravida as the woman who at the beginning of a pregnancy weighs 10 per cent or more over her ideal theoretical weight. The author discusses the various complications associated with obesity in pregnancy: tendency to abortion, fetal death in utero, extreme difficulty in palpation and auscultation, diagnosis of dystocia, and prolonged labor. He draws attention to the association of obesity, fetal giantism, and diabetes as a syndrome. The dietary management of the obese gravida is discussed in some detail. The author recommends a high protein intake, with avoidance of bread, starches, sugar, and alcohol, together with minerals and vitamins as necessary to fulfill normal requirements. During the first four months of pregnancy, the author recommends restriction of the diet in an attempt to approach the patient's ideal weight. After the middle of the fourth month, he allows no more than 2 kilograms per month weight gain up to the eighth month, and in the ninth month of gestation he maintains the weight reached at the eighth. Two standard reduction diets are detailed: a 1,200 calorie diet with 90

grams of protein, and a 1,460 calorie diet with 123 grams of protein. Specific clinical data are not provided but the author indicates that these regimens have been useful in his practice.

DOUGLAS M. HAYNES, M.D.

Vol. 33, September 23, 1954.

Zuckermann, Conrado: Lymph Node Dissection and Hysterectomy for Cancer of the Cervix Uterine, p. 295.

*Imaz, F. A. Uranga, de Gómez, N. Gil, and Roca, H.: Severe Toxemia Treated by Artificial Hibernation, p. 303.

Caso, Rogelio, and Di Fonzo, Normando O.: Local Anesthesia in Cesarean Section, p. 316.

Nogues, Armando E., Guixa, Hector L., and Otturi, Juan E.: Indications and Selection of Androgens in the Treatment of Dysmenorrhea, p. 324.

Uranga Imaz, de Gómez, and Roca: Severe Toxemia Treated by Artificial Hibernation, p. 303.

Artificial hibernation as a mode of therapy for severe forms of the pre-eclampsia syndrome was first suggested in 1953 by Aoustin, and was promptly documented by the appearance of several articles in the French literature; these are briefly summarized in this report. The authors then add reports of two patients, one with severe pre-eclampsia and the other with true eclampsia, treated by an artificial hibernation regimen in conjunction with intravenous administration of fairly large amounts of isotonic solutions and sympatholytic agents. Both patients survived and were delivered vaginally of live infants. The authors describe their method of packing the patients in ice, and suggest that the artificial hibernation principle, if maintained for ten hours or longer, may have some value in the empirical clinical treatment of specific pregnancy toxemia.

DOUGLAS M. HAYNES, M.D.

Vol. 33, October 21, 1954.

Foglia, Virgilio G.: Ideas Regarding the Chemistry and Physiology of the Androgens, p. 367.

Staffieri, Juan Jose: The Physiopathological Basis of Androgen Therapy in the Woman, p. 372.

*Murray, Edmundo G.: Indications for and Results of Androgen Therapy in Women, p. 377.

Murray: Indications for and Results of Androgen Therapy in Women, p. 377.

The author summarizes a broad experience in the use of androgenic substances for various gynecologic conditions. In general, complete neutralization of estrogenic activity was observed when the doses exceeded 400 mg. per month. Masculinizing effects appeared in the following order: acne, leukorrhea, vulvar congestion, hypertrichosis, clitoridal hypertrophy, and voice changes. The author found that careful records of the basal temperature, vaginal cytologic smears, observations on crystallization of cervical mucus, endometrial biopsy, and determinations of 17 ketosteroids, pregnanediol, and hypophyseal gonadotrophins were useful in following patients under androgenic therapy.

The principal results were the following: 73 per cent of 64 patients with premenstrual tension exhibited favorable results shortly after androgen therapy, but improvement persisted longer than six months in only 28 per cent. Sixty-eight per cent of 51 women with dysmenorrhea responded satisfactorily to androgen therapy. In 62 patients treated for various types of functional metrorrhagia, favorable results were obtained in 72 per cent; in this condition, doses varying from 150 to 250 mg. per month showed temporary clinical improvements in 8, but the symptoms recurred in full force as soon as the medication was discontinued. Seventy-five per cent of a large series of puerperal patients showed significant diminution in lactation when androgens were administered beginning

on the third or fourth puerperal day. Oral administration of androgen starting immediately after delivery produced excellent results in 91 per cent. Eleven patients with advanced carcinoma of the breast were treated with androgens, and in 9 of them there was remission of pain and general systemic improvement. The dosage used in these patients was high (500 to 600 mg.). Women with symptoms of the climacteric were treated with androgens and beneficial effects were obtained in 64 per cent. When progesterone and androgens were combined the results were noticeably improved.

The author lists the following contraindications to androgen therapy: estrogen deficiency states manifested clinically by menstrual alteration or genital hypoplasia; clinical signs of defeminization or masculinization preceding therapy or occurring during therapy; pregnancy; and advanced postmenopausal involutional states.

DOUGLAS M. HAYNES, M.D.

Vol. 33, October 28, 1954.

Margulies, Miguel: Obstetrical Management of the Rh Negative Woman, p. 385.

Albertelli, Jorge F., Monaco, Horacio, and Cetrangolo, Jose M.: Bilateral Adrenalectomy in Advanced Cancer of the Breast, p. 393.

Uranga Imaz, Francisco A.: Total Detachment and Primary Expulsion of the Placenta Previa, p. 402.

*Peralta Ramos, Alberto G., and Goni, Miguel A.: Vaginal Hysterectomy for Genital Prolapse of Elderly Women, p. 407.

Peralta Ramos and Goni: Vaginal Hysterectomy for Genital Prolapse of Elderly Women, p. 407.

Professor Peralta Ramos and his co-worker report their results in 27 patients between the ages of 51 and 83 years subjected to vaginal hysterectomy for the treatment of genital prolapse. In all these women vaginal plastic repairs were performed at the time of vaginal hysterectomy. Satisfactory results were obtained in 92 per cent of these patients, even though only 68 per cent exhibited a perfect anatomical result. The authors point out that vaginal hysterectomy alone does not of itself cure genital prolapse unless the appropriate plastic repair is carried out. Most of the operations were performed under local anesthesia with 1 per cent Novocain to which a few drops of Adrenalin had been added. Occasionally, small doses of Pentothal sodium were necessary. The combination of vaginal hysterectomy with plastic repair is indicated, in the opinion of the authors, only when the hysterectomy is specifically necessitated by some uterine lesion requiring excision. They prefer to perform the Manchester operation for the cure of genital prolapse in most of these patients. No mention is made of the LeFort colpocleisis, which the authors apparently do not favor.

DOUGLAS M. HAYNES, M.D.

Vol. 33, November 4, 1954.

Ortiz, N. Contreras, Sanmartino, R., and Zucotti, A. S.: Melanoblastoma of the Ovary 14 Years After an Ocular Tumor, p. 427.

*Peiretti, Francisco S., and Korembli, Eugenio: ACTH in the Treatment of Shock in Obstetrics, p. 433.

Lienhard, Carlos P.: Critical Analysis of 27 Cases of Carcinoma of the Endometrium and the Long-range Results of Its Treatment, p. 441.

Vaira, Andres, and Salerno, Enrique: Treatment of Feminine Frigidity With Androgens, p. 449.

Pereyra, Emilio D., Gorelik, Naum, Eguia, Osvaldo F., and Sardi, Juan Luis: Brenner Tumor of the Ovary Associated With Carcinoma in Situ of the Cervix, p. 457.

Peiretti and Korembli: ACTH in the Treatment of Shock in Obstetrics, p. 433.

Since they assume that shock in obstetrics often represents an alteration of the alarm reaction of Selye due to failure of the suprarenal cortex with consequent diminution in

the production of ACTH, the authors believe that ACTH has some place in the treatment of many cases of shock in obstetrics. Sixteen patients are reported upon here who were treated for shock of various types. The hormone was administered intravenously in a solution containing 25 units of ACTH per 500 c.c. of isotonic glucose administered at the rate of 60 to 100 drops per minute, or in conjunction with blood transfusion. The symptomatology of the patients so treated consisted of arterial hypotension with lowering of the pulse pressure, sweating, pallor, and thready pulse. The authors admit that the administration of whole blood alone in many cases might have produced the recuperation of the patient, even if ACTH had not been used. They state, however, that with the use of ACTH immediate and dramatic improvement occurred in several patients after only 50 to 100 c.c. of blood had been given, and that in their opinion this would not have been the case if blood alone had been administered. Similar results were obtained, moreover, when ACTH was injected in isotonic glucose solution. Fifteen of the 16 patients recovered; only one patient in the series died, and that patient had a postpartum coagulation defect. The authors do not give sufficient obstetrical data to make it possible to assess the exact etiology of the shock in the 16 cases reported, so that objective evaluation of their results is difficult.

DOUGLAS M. HAYNES, M.D.

Bordeaux surgical

Vol. 3, July, 1954.

*Magendie, Reboul, Delorme, Pérotin, and Herpé: Pneumopelvography and Gynecography in Gynecology, p. 117.

Pétrait, A., Cornet, L., Tessier, R., and Casting, R.: Fibromas of the Visceral Pleura and of the Left Superior Lobe, p. 124.

Massé, C.: Problems of Homografts, p. 128.

Magendie, J.: Bile Peritoneum by Transudation, p. 141.

Massé, L., and Pellet, C.: Brief Curare-like Action of Succinylcholine, p. 143.

Magendie, Reboul, Delorme, Pérotin, and Herpé: Pneumopelvography and Gynecography in Gynecology, p. 117.

Pneumopelvography is the term used to demonstrate the outline of the female pelvic organs by x-ray, using intraperitoneal injection of gas for the contrast medium. Gynecography, in contradistinction, utilizes intrauterine opaque fluids to produce visualization. The former has the advantage of being able to demonstrate the external shape and size of all the pelvic organs, the latter of showing only the internal formation of the uterine cavity and Fallopian tubes.

This article deals essentially with the technique, indications and contraindications for, and results of, pelvic pneumoperitoneum. The technique is simple. One and a half to two liters of carbon dioxide gas are introduced, by means of a fine needle in the iliac fossa, into the peritoneal cavity. The patient is then placed on the x-ray table, on her chest, in the Trendelenburg position, and the necessary photographs taken. The gas is absorbed in several hours and the patient may resume her activities. This procedure is contraindicated in cases where cardiac decompensation, pelvic inflammatory disease, or pregnancy (after the fifth month) is present.

By means of this procedure, the external form of the uterus, the round ligaments, and the form and volume of both ovaries are easily discernible. Pathological states including ovarian tumors, ovarian cysts, and fibromas of the uterus can be visualized, as well as all malpositions of the genital organs. Pneumopelvograms can be made in conjunction with hysterosalpingography easily and safely. The method is safe and is an excellent means for confirming a difficult diagnosis where other methods are noncontributory.

L. B. WINKELSTEIN, M.D.

The British Medical Journal

Vol. 2, December 18, 1954.

Butter, N. R., and Martin, J. D.: Anemia of the Newborn Following Anterior Placenta Previa, p. 1455.

Vol. 1, January 1, 1955.

*Rosenthal, Leonard: Coarctation of the Aorta and Pregnancy, p. 16.

Thomson, A. M.: The Epidemiological Approach to Obstetric Medicine, p. 19.

Rosenthal: Coarctation of the Aorta and Pregnancy, p. 16.

The coexistence of coarctation of the aorta with pregnancy is rare. Prior to this report 91 cases are found in the literature. The author adds 5 cases, 2 of which terminated by rupture of dissecting aneurysms.

In a review of the 91 cases in the literature it was ascertained that in 6 instances rupture of the aorta occurred at term or during labor. Some patients have withstood multiple pregnancies without incident.

The degree of hypertension or of collateral circulation appears to be of no prognostic value. Management is varied, depending upon the physician handling the case. It is suggested that a high index of suspicion be entertained in order that the diagnosis may be established at the onset of pregnancy and the patient referred to a thoracic unit for definitive treatment. Diagnosis later in pregnancy is best managed as if the patient were suffering from rheumatic heart disease.

Aneurysmal aortic dilatation, megalocardia, or symptoms of cerebral aneurysm may indicate that pregnancy should be terminated. A rise in blood pressure in the last few weeks of pregnancy should be considered an additional warning of a possible impending catastrophe.

ARTHUR PERELL, M.D.

Vol. 1, January 8, 1955.

Campbell, P. E.: Sudden Death in Labor After Penicillin Injection, p. 87.

Vol. 1, January 15, 1955.

*Joske, R. A.: Pancreatitis Following Pregnancy, p. 124.

Joske: Pancreatitis Following Pregnancy, p. 124.

Pancreatitis following a recent pregnancy may represent a distinctive syndrome of pancreatic pathosis. Including 6 additional cases of the author there have been 68 reports in the literature of this condition. The author reviews the literature, presents the new cases, and discusses various aspects of the problem.

The important features of the previously unreported cases are presented in table form. All 6 patients showed an increased amount of bile in the urine, 2 showed glycosuria, and 2 proteinuria. Urinary diastase levels ranged from 30 to 2,000. The diagnosis was confirmed in the individual with the lowest reading by laparotomy.

Four of the patients demonstrated cholelithiasis. This may be an etiological factor. Reflux of bile into the pancreatic duct may have been the basis of the disease in 2 patients.

Although the mechanism of production is unknown, the disease must be suspected in the young postparturient complaining of flatulence, recurrent abdominal pain, and gastrointestinal upset.

The bibliography is adequate.

ARTHUR PERELL, M.D.

Vol. 1, January 29, 1955.

*Morris, W. I. C.: Management of Eclampsia, p. 279.

Morris: Management of Eclampsia, p. 279.

This is part of a series of collected articles comprising a refresher course for the general practitioner. The problem of the treatment of the eclamptic patient in England is reviewed. A large percentage of the patients are treated on a domiciliary basis.

The general management consists of a modified Stroganoff regime, good general nursing, and in the case of eclampsia with convulsive seizures: (1) maintenance of a patent airway, (2) nonstimulation, (3) antibiotics, (4) oxygen and digitalis when indicated. Intervention with gestation should, if possible, be reserved for late in the second stage of labor. The author feels that cesarean section is contraindicated unless other indications are present.

First aid includes intravenous barbiturates, chloroform anesthesia, and, after the seizure, morphine should be administered and the patient transported to a medical center. Air travel is not contraindicated where necessary.

Should institutionalization be impossible the author outlines a basic schedule for treatment including morphinization, intravenous barbiturates, magnesium sulfate, intravenous glucose solution, and if necessary certain hypotensive drugs.

This article is essentially one of basic therapeutics and may be of value to the practitioner in an isolated community.

ARTHUR PERELL, M.D.

Vol. 1, February 5, 1955.

*Cocks, Denis Pells: Significance of Initial Condition of Cervix Uteri to Subsequent Course of Labor, p. 327.

Cocks: Significance of Initial Condition of Cervix Uteri to Subsequent Course of Labor, p. 327.

This article is a study of 133 cases not complicated by cephalopelvic disproportion, in which the condition and type of cervix at the time of attempted induction of labor were correlated with the subsequent termination of gestation. There were 5 groups of cervixes categorized. Two of the 5 were considered to be "ripe" for induction and the rest were "unripe." Every group was subdivided into those in which the os was in the mid-position, and those presenting a posterior or sacral os.

Tables are presented to illustrate the average time from induction to delivery, the average duration of labor, and the method of termination when operative intervention seemed indicated. In the discussion of the presented data the author states that careful examination of the cervix prior to induction of labor should enable the operator to estimate reasonably the likely course. Regardless of "ripeness," if the position of the cervix is posterior, a longer average latent period prior to the onset of labor should be anticipated. Once this has passed, however, the hours of actual labor should equal those in normal cervical position. Methods of correcting the sacral os are suggested.

It is the opinion of the reviewer that this important problem of inducibility is frequently paramount and studies such as this one are certainly worth while. The author should be encouraged to enlarge his series and perhaps to include factors of parity and fetal size.

ARTHUR PERELL, M.D.

Vol. 1, February 12, 1955.

Fischer, M., and Biggs, R.: Iron Deficiency in Pregnancy, p. 383.

Vol. 1, March 26, 1955.

*Wynder, Ernest L.: Environmental Factors in Cervical Cancer, p. 743.

Wynder: Environmental Factors in Cervical Cancer, p. 743.

In an effort to evaluate the role of preventive measures in the field of cervical malignancy, Dr. Wynder has conducted a clinical investigation of various extrinsic factors in different population groups. If one accepts the validity of his sources of statistics, many significant conclusions can be made from the study.

As previously known, the incidence of cancer of the cervix was observed to be 60 per cent higher among Negroes than among whites in the United States. In addition, the rate among Jews was only one-fifth to one-tenth that of the non-Jewish women. The relative frequency among Hindu women was 45 per cent, Indian Christians 29 per cent, Moslems 18 per cent, and Parsees 16 per cent. For the purpose of analysis, 892 patients with cervical cancer were carefully interviewed, as well as a control group of 1,826 patients with other pelvic disturbances. Not only were fewer single women seen among patients with cancer of the cervix, but also cervical cancer patients were found to marry more frequently than the control group. Although the cancer group married earlier, early coitus was of greater significance. For the non-Jewish white cervical cancer group, it was 19 per cent before the age of 16 and for the controls 10 per cent. Respective data for the Negroes were 55 per cent and 36 per cent, and for the Jewish group 15 per cent and 4 per cent.

Circumcision was clearly demonstrated to be an important extrinsic factor. For the white non-Jewish group 5 per cent of the patients reported exposure only to circumcised males, as compared with 14 per cent of the controls. For Negroes the respective percentages were 0.5 per cent and 9 per cent. The age of circumcision did not seem of importance so long as it occurred before marriage. Aside from the circumcision per se, penile hygiene itself is important as indicated by the fact that those male groups have the highest degree of poor penile hygiene whose females have the highest rates of cervical cancer.

The author concludes that exogenous factors play a major part in the development of epidermoid cancer of the cervix. The data would indicate that universal circumcision may be a "practical preventive step, significantly reducing the incidence of cervical cancer."

JOHN G. MASTERSON, M.D.

Vol. 1, April 2, 1955.

Kouyoumdjian, Alex: Pelvic Tuberculosis, p. 829.

Vol. 1, April 9, 1955.

Pengelly, C. D. R.: Pneumococcal Meningitis, p. 870.

Bulletin Algérien de Carcinologie

Vol. 21, First Trimester, 1954.

Marie, R.: Gastric Cancer in Algeria, p. 5.

Schweitzer, J.: Study of Sahara Carcinoides, p. 21.

*Combescot, C., Reviere, M., and Audibert, A.: Relation of Testosterone to Progesterone in the Development of the Decidua in the Castrated Rabbit, p. 23.

*Reviere, M.: Mammary Proliferation in the Adult Male Monkey Caused by Estrogen Pellet Implantation, p. 25.

Sitbon, J., and Viel, R.: Laryngectomy for Laryngeal Cancer in Pulmonary Tuberculosis, p. 29.

Combescot, Reviere, and Audibert: Relation of Testosterone to Progesterone in the Development of Decidua in the Castrated Rabbit, p. 23.

Although the roles of estrogens and progesterone in the formation of a decidual reaction of the endometrium are well established, the effects of testosterone are not so well understood. Testosterone has been shown to be of importance in the development of the placenta. The authors have, on an experimental basis, using castrated rabbits, assayed the

value of male hormone on the endometrium. Using daily doses of 5 mg. of progesterone and 1 mg. of testosterone (as replacement for follicular hormone) they were able to demonstrate that these hormones acted as synergists in the production of true decidual reactions of the endometrium.

L. B. WINKELSTEIN, M.D.

Riviere: Mammary Proliferation in the Adult Male Monkey Caused by Estrogen Pellet Implantation, p. 25.

Estrogens have been found to produce, in animals, both benign and malignant tumors of the breast. This observation has never, however, been proved in the human being. To answer the question whether follicular hormone by itself has this effect, the author implanted pellets of estrogenic hormone into adult male monkeys. The process was carried out for periods of time varying from several weeks to almost two years. He noted that the mammary gland as well as the sexual skin area of the monkey hypertrophied markedly after the implantation of these pellets. Microscopically this proliferation was noted in the acini of the glands. However, even after therapy for long periods of time neither benign nor malignant growths were observed to develop.

L. B. WINKELSTEIN, M.D.

Wiener klinische Wochenschrift

Vol. 66, No. 29, July 23, 1954.

*Ellegast, H., Gumpesberger, G., and Wewalka, F.: The Effects of Hepatitis in Pregnancy on the Infant, p. 507.

Ellegast, Gumpesberger, and Wewalka: Effects of Hepatitis in Pregnancy on the Infant, p. 507.

The authors discuss 57 cases of icterus in pregnancy, in 2 of which stillborn infants were produced, and in 4 immature babies that died the first day. Of the remaining 51, only one infant developed jaundice and that was at seven days of life.

Twenty-five mothers developed hepatitis after delivery. Among these cases, one baby died at 6 months of age of acute yellow atrophy and one died at the age of 6 weeks of enterocolitis. The others were all well.

Among 43 mothers who had hepatitis shortly before conception, only two babies were born with anomalies. The cause-and-effect relationship is questionable, however.

The authors believe that there is greater danger in homologous serum jaundice than in epidemic hepatitis.

WALTER F. TAUBER, M.D.

Vol. 66, No. 49, December 10, 1954.

Bauer, K., and Schumann, F.: Reevaluation of Rapp and Richardson's Sex Determination of the Unborn Child, p. 939.

Vol. 66, No. 51, December 24, 1954.

Homma, H.: Malignant Tumors of the Ovary, p. 969.

Zentralblatt fuer Gynäkologie

Vol. 76, No. 13, 1954.

Fauvet, E.: Therapeutic Results With the Radical Vaginal Hysterectomy and Discussion of Accidental Operative Injuries, p. 481.

*Huber, H.: Primary Mortality, Morbidity, and Accidental Injuries Encountered in the Surgical Treatment of Carcinoma of the Cervix, p. 488.

*Fochem, K., and Kofler, E.: Therapeutic Results in Carcinoma of the Fundus From 1943 to 1948 at the First Frauenklinik (Women's Hospital) of the Vienna University, p. 494.

Schubert, E. V.: Sarcoma of the Pelvic Connective Tissue, p. 501.

Geipel, K.: The Incurable Carcinoma of the Uterus, p. 504.

Tosetti, K.: Extract of Mistletoe and Vitamin A in the Treatment of Female Genital Cancer, p. 509.

Verhagen, A.: Radium Introducer for Intrauterine Radium Application, p. 514.

Ganse, R.: Epithelial Changes of the Small Labia in a Case of Carcinoma of the Vulva, p. 516.

Huber: Primary Mortality, Morbidity, and Accidental Injuries Encountered in the Surgical Treatment of Carcinoma of the Cervix, p. 488.

This report from the gynecological hospital of the University of Kiel covers the period from 1922 to 1952. In this period 741 vaginal and 273 abdominal radical hysterectomies were performed. The primary mortality of the vaginal radical operation was 3.6 per cent and of the abdominal 14.2 per cent. The total number of serious postoperative complications is shared among the vaginal and abdominal operations as follows: thrombosis-embolism 19 against 11, bronchopneumonia 1 against 5, cystitis-pyelitis 1 against 7, wound infection 11 against 7 and postoperative hemorrhage 4 against 0. The incidence of accidental operative injuries to bladder, ureter, rectum, and of necrosis of the denuded ureter is higher in the vaginal operation, 3.1 per cent against 1.8 per cent in the abdominal operation. The individual cases do not lend themselves to abstracting. It may be mentioned, however, that all injuries to the bladder and rectum healed per primam. In only two cases was the injury to the ureter the direct cause of late operative death.

H. L. LUSCHINSKY, M.D.

Fochem and Kofler: Therapeutic Results in Carcinoma of the Fundus From 1943 to 1948 at the First Frauenklinik (Women's Hospital) of the Vienna University, p. 494.

The treatment of choice was the abdominal hysterectomy with bilateral salpingo-oophorectomy. The report concerns 104 cases. Seventy per cent of the patients were 46 to 65 years old. Thirty-nine per cent were nulliparous women. Metrorrhagia was present in 94 per cent, and loss of weight in 46 per cent. The five-year cure in the 79 cases operated upon was 81 per cent with an operative mortality of 1.25 per cent. Primary radium was given to 23 patients who were either inoperable or had distant metastases or presented medical contraindications. The five-year survival of this group was 26 per cent. Additional x-ray therapy was given in 86 per cent of all treated cases. In 7 cases operated upon the ovaries were not removed. The reasons for this were that in 5 cases the carcinoma was not suspected at the operation, in one case the ovaries were too adherent to be safely removed by the vaginal route, and in one case they were not removed because of extreme youth. All these 7 cases had five-year cures. The total cure rate of the entire series was 67.3 per cent. Histological analysis of the available material showed adenocarcinoma in 61 cases, a mixed solid and adenomatous carcinoma in 17 cases, solid carcinoma in 10, squamous carcinoma in one, adenocarcinoid in 12, and adenoma malignum in 3 cases. In the 72 cases with surgical removal of the adnexa there was only one case with metastasis to the mesosalpinx and none with ovarian involvement.

H. L. LUSCHINSKY, M.D.

Vol. 76, No. 18, 1954.

*Stange, H. H., and Drescher, J.: Further Experimental Contributions to the Problem of Peripheral Neurosecretion, p. 697.

Taomergen, H. S.: Quantitative and Qualitative Determination of Serum Albumen in Cases With Suspicious Erosion of the Cervix, p. 701.

Bruntsch, K. H.: Intraperitoneal Hemorrhages in Patients With Connective Tissue Tumors of the Uterus, p. 706.

Manzack, R.: A Case of Inversion and Torsion of a Myomatous Uterus, p. 713.

Sederl, J.: Contribution to the Treatment of the Uterine Myoma, p. 717.

Stange and Drescher: Further Experimental Contributions to the Problem of Peripheral Neurosecretion, p. 697.

The formation of vacuoles within the protoplasm of peripheral vegetative ganglia was first interpreted as neurosecretion by Gaupp in 1937. This interpretation is supported by the present work. In experiments on pregnant rats the authors showed that peripheral ganglionic blockage by Pendiomid (Ciba) is followed by a significant decrease of the vacuolization in the ganglia of the Frankenhäuser plexus. They also noted that the period of gestation in the blocked animals was prolonged from 21 to 24 days. An increase in the vacuolization could be obtained by electric stimulation of the Frankenhäuser plexus.

H. L. LUSCHINSKY, M.D.

Vol. 76, No. 22, 1954.

*Lax, H.: Some Histological Rarities, p. 849.

Frank, E., Froewis, J., Rockenschau, A., and Ulm, R.: Treatment of Menopausal Symptoms by Combined Estrogen-Androgen Depot, p. 859.

Gosch, J.: Contribution to the Treatment of Menopausal Bleeding by Radioactive Cobalt, p. 868.

Heisz, H.: Primary Chorionepithelioma of the Tube, p. 870.

Mencken, F.: A Stereocolpophotoscope to Record Surface Changes of the Cervix, p. 874.

Lax: Some Histological Rarities, p. 849.

The author describes three rarities: the metastasis of a tubal carcinoma to the endometrium via mucous membrane, a very early corpus luteum abscess, and a carcinoma of the Bartholin gland. He states that implantation of cancerous cell groups on the intact surface of the genital mucosa is rare. In the described case the protection against implantation was diminished inasmuch as the endometrium of this 47-year-old patient was atrophic and partially cystic. The implant occurred on the surface of a cystically dilated endometrial gland of the fundus, with only a very scant stromal contact of the implant. Adjacent lymphatics and musculature of the fundus were free from metastases; the isthmic part of the tubal lumen showed an intact mucosa. The second case concerns a very early corpus luteum abscess which occurred after intrauterine instrumentation, but in absence of tubal participation and many days after the ovulation, and which therefore was probably due to hematogenic transmission.

The third case concerns a primary carcinoma of the Bartholin gland which imitated the histological picture of a squamous carcinoma of the cervix. This histological type is explained on the basis of the frequently found epidermization of the preglandular duct which occurs as a result of an inflammation.

H. L. LUSCHINSKY, M.D.

Correspondence

Disadvantages in Use of Tantalum Mesh in Repair of Cystocele

To the Editors:

In an article published in the May number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Drs. Moore, Armstrong, and Wills reported on the use of tantalum mesh in the repair of cystocele. They were evidently influenced by the reports in the surgical journals of the use of that metal mesh in the repair of certain types of hernia. It is only fair to state that that method was resorted to in only a very limited number of cases and only in those recurrent cases in which repeated efforts failed to cure the hernias, and, perhaps in desperation, tantalum mesh was used to cover the defect. The results have not always been happy ones. In many cases the metal mesh broke down, crumbled into many fragments. In some cases infection occurred and the metal mesh was hanging loose in the wound. In other cases the wire ends were found sticking out of the wound.

As to the procedure practiced by the authors, I hope they will not encounter much trouble with it; but, in reading the article, I was impressed by the fact that in four out of nine cases the results were not so good. In some, the tantalum was exposed in the wound and, they state, was covered with granulation tissue. Surgically speaking, this may mean there had been some sloughing of part of the vaginal wall, due, as they rightly surmise, to ischemia. A foreign body in living tissue is likely to cause trouble anywhere, but especially when the vaginal wall is split into two layers, as they indicate, causing interference with nutrition of the outer layer.

What will happen in those cases when the metal mesh breaks up and the wire ends are sticking out in the wound? And, in the cases of the not too old people, what about the male partner under certain conditions? Might it not be a cause for a malpractice suit?

HERMAN SHANN, M.D., F.A.C.S.

277 EASTERN PARKWAY
BROOKLYN 38, N. Y.
JUNE 18, 1955

Another Case of Annular Detachment of the Cervix During Labor

To the Editors:

I have recently read in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, volume 70, page 193, 1955, the case reported by Drs. James H. Tisdell and Paul S. Andreson, entitled, "Spontaneous Annular Detachment of the Cervix During Labor," mentioning 55 cases related up to 1947.

In 1950, I presented at the Third Spanish-Portuguese Congress of Obstetrics and Gynecology at Barcelona a similar case, treated at the Maternity Section of the Medical School Hospital, Goa, Portuguese India, of annular detachment of the cervix during labor due to the circular necrosis provoked by compression and tetany of the uterus resulting from abnormal dosage of Pituitrin, injected before the patient's admission to the Maternity Hospital. This case was published in Portuguese in the *Clinical Review of Maternal Institute* at Lisbon (Rev. Clin. Inst. Mater. 3: 33, 1951).

I take pleasure in sending you two copies of my article referred to and a translation into English. One of them is intended for the files of your JOURNAL and I shall be obliged if you will send the other to Dr. Tisdell and Dr. Andreson.

Thanking you for your kind attention to my request, I remain

Yours sincerely,

JOÃO FILIPE DO RÊGO

PROFESSOR OF OBSTETRICS AND GYNECOLOGY

ESCOLA MÉDICO-CIRÚRGICA DE GOA

GOA

PORTUGUESE INDIA

OCT. 20, 1955

Item

British Society for Study of Fertility

The British Society for the Study of Fertility will meet in London, England, June 14 and 15, 1956. For information write to the Secretary, Mr. H. H. Fouracre Barns, 31 Weymouth Street, Portland Place W 1, London, England.

Second World Congress on Sterility and Fertility

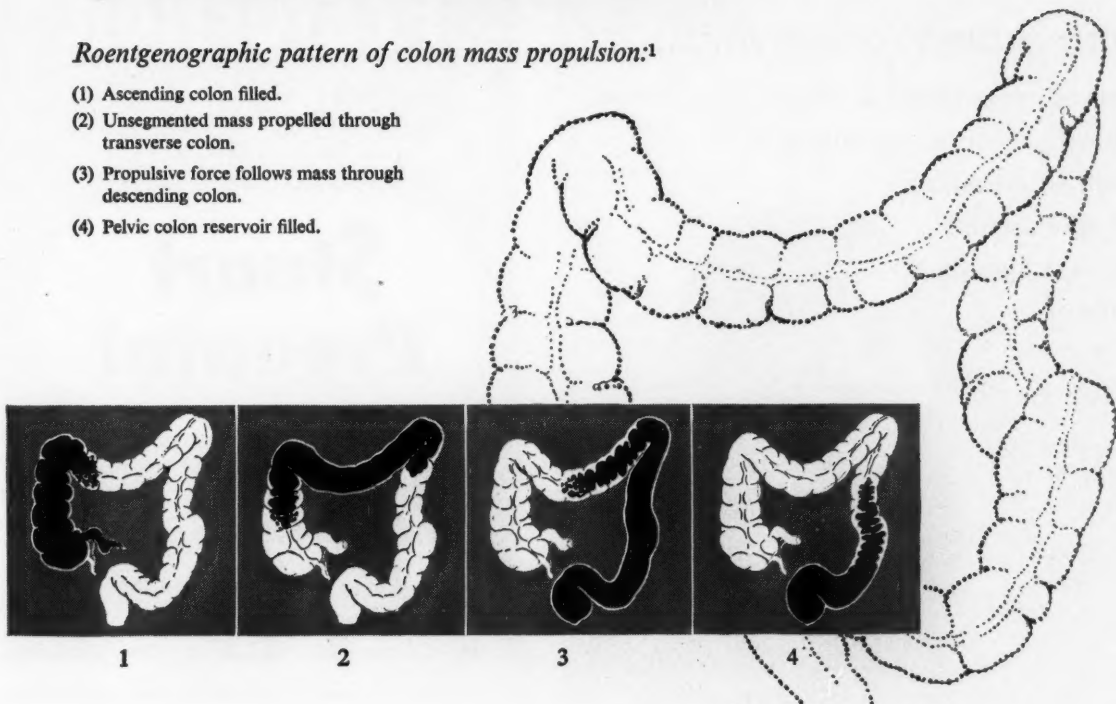
The Second World Congress on Sterility and Fertility of the International Fertility Association will be held in Naples, Italy, May 18 to 25, 1956. About 180 scientific papers covering all phases of infertility are scheduled to be presented. All interested physicians are invited to attend.

For information regarding travel, registration, and hotel accommodations, write to Dr. Maxwell Roland, Chairman, Liaison Committee, 1141 Eastern Parkway, Brooklyn 13, N. Y.

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mands adequate intake of fluids (one glass with Metamucil powder, one glass after each dose); it increases the physiologic demand to evacuate; and it does not establish a laxative "habit." Metamucil, in addition, is inert, and also nonirritating and nonallergenic.

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1. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice: A Text in Applied Physiology*, ed. 5, Baltimore, The Williams & Wilkins Company, 1950, pp. 579-583.

2. Bergen, J. A.: A Method of Improving Function of the Bowel, *Gastroenterology* 13:275 (Oct.) 1949.

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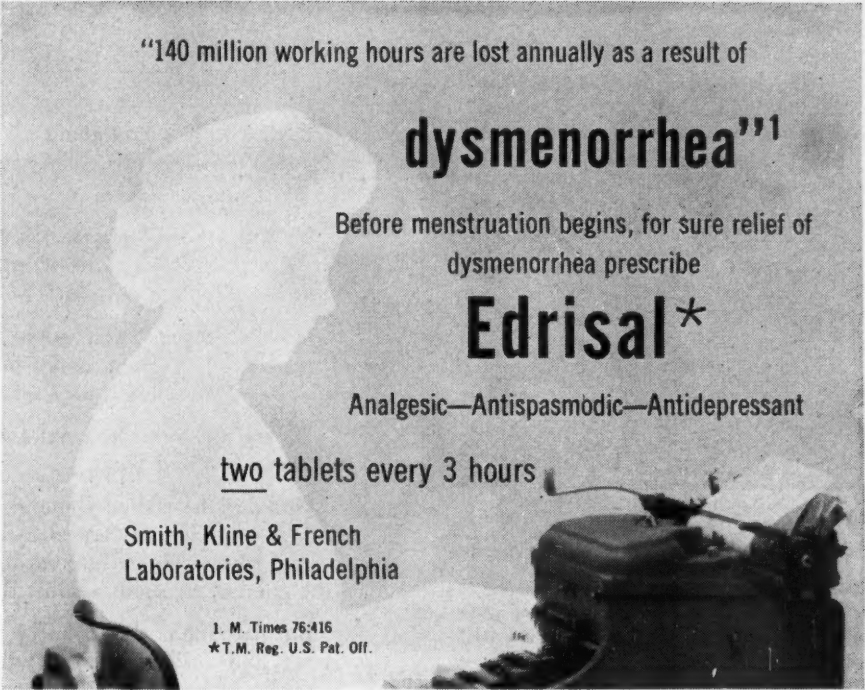
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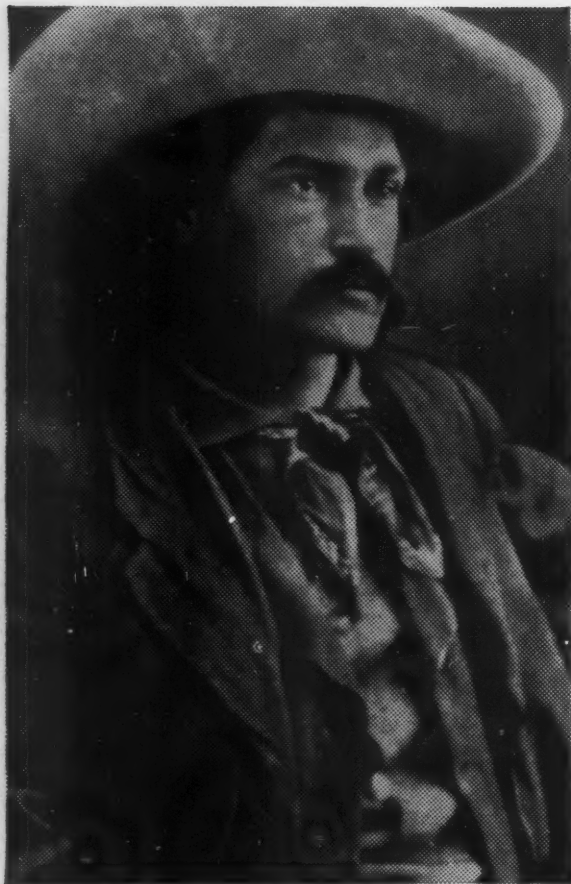
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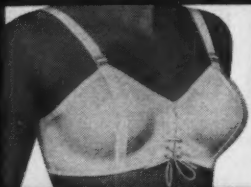
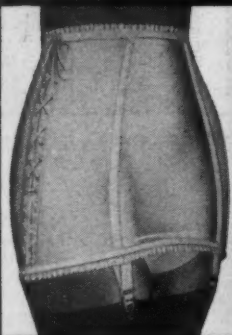
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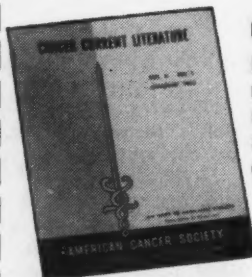
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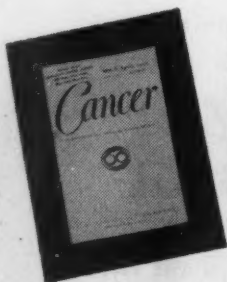
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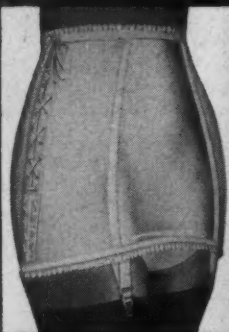
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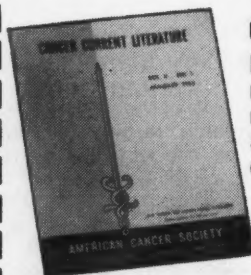
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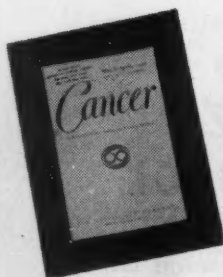
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